



THE LIVERPOOL RESPIRATORY BIRTH COHORT STUDY

Questionnaire Development, Recruitment and
Preliminary Results

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Errata

The following amendments have been made to this thesis following Viva Voce examination on the 26th of September 2013.

Section 1.2 The Burden of Respiratory Disease. This section discusses the indirect impact of respiratory disease upon children and their families, as well as the significance and benefits for clinicians and families of measuring this impact. **(Pages 15-16)**

Section 1.3.5 Review of Birth Cohort Study design: This section now includes a critical appraisal of birth cohort study design. **(Page 35)**

Section 3.5.2 Methods: Now clarifies and explains the testing order of SelectSurvey.NET and Adobe FormsCentral on mothers during the second feasibility study. **(Page 75)**

Section 4.2.3 Results: This section has been amended to contain 95% confidence intervals for the recruitment rates reported in the four week recruitment pilot. **(Pages 90-92)**

Section 4.2.4 Discussion: The discussion in this section has been amended to reflect the changes in the range for the true population value in Section 4.2.3. **(Pages 92-93)**

Section 5.3.4 The Liverpool Respiratory Symptom Questionnaire: This section discusses the current limitations of the analysis of LRSQ symptom domain scores in comparison to the scores in the quality of life domains, and explains that this analysis has yet to be validated. **(Pages 120-121)**

Section 5.4.7 Limitations: This section appraises the potential bias of the seasonality of respiratory symptoms in the analysis of results due to the increased prevalence of both infectious and non-communicable causes of symptoms during the winter months. **(Page 127)**

Section 6.1 Discussion The discussion further explores the possible causal relationship linking social deprivation and respiratory disease, and suggests how the LRBCS may be able to distinguish between competing theories. **(Page 131)**

Additionally, minor spelling and grammatical errors have been corrected throughout this thesis.

I. Abstract

Background The Liverpool Respiratory Birth Cohort study (LRBCS) is a prospective, longitudinal population based birth cohort study of respiratory symptoms in preschool children domiciled within Liverpool postcodes L1-L38 at the time of birth. Researchers personally recruit new mothers to the study during their stay at Liverpool Women's Hospital. The study uses either an online or paper version of the parent-completed Liverpool Respiratory Symptom Questionnaire (LRSQ) to investigate the prevalence of respiratory symptoms, such as coughs, colds and wheezing alongside an exposures and demographics questionnaire.

Aims and Objectives To further develop the concept of the LRBCS; to finalise the content and design of questionnaires and research materials for the study, as well as test the feasibility of conducting the study online. A further aim was to identify the most effective recruitment strategy for the study and then to proceed recruiting mothers to the LRBCS. The final objective was to conduct preliminary analyses of results from the initial questionnaire.

Methods Research students performed two feasibility studies and developed the appearance and content of questionnaires with input from mothers. Expression of interest were obtained from eligible mothers on the postnatal wards at Liverpool Women's Hospital. Mothers provided full consent and fully enrolled their child when he or she was aged four months. Questionnaires were distributed by automated emails or by post. Returned questionnaires were analysed by descriptive statistical methods. The internal validity of the LRSQ was assessed by calculating Cronbach's alpha coefficients to assess internal validity.

Results 1685 expressions of interest were received from eligible mothers between January and June 2014. 177 questionnaires were returned to the research team. There was a 25% participation rate (33% online and 7% postal). Preliminary analysis demonstrated some differences between participants and the general Liverpool population; mothers who respond were older, more educated, more likely to breastfeed and less likely to smoke cigarettes. Children exposed to household cigarette smoke had significantly higher LRSQ scores than those who were not exposed, which indicated that these children have a higher prevalence of respiratory symptoms. Seven out of the eight domains of the LRSQ had acceptable-excellent internal validity.

II. Acknowledgements

This thesis would not have been possible without the ongoing help and support from so many people that I have been fortunate enough to have in my life during the last year.

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IV. Table of Abbreviations

AFC	Adobe® FormsCentral
ALSPAC	Avon Longitudinal Study of Pregnancy and Childhood 1991
API	Application
ATS	American Thoracic Society
BCS70	British Birth Cohort Study 1970
CLS	Centre for Longitudinal Studies
DDA	Doctor Diagnosed Asthma
ELSPAC	European Longitudinal Study of Pregnancy and Childhood
G	Grams
GA²LEN	Global Asthma and Allergy Excellence Network
GP	General Practitioner
HSCIC	Health and Social Care Information Centre
HMO	Health Maintenance Organization
HTML	Hypertext Markup Language
ID	Identification
IP	Internet Protocol
IMD	Indices of Multiple Deprivation
ISAAC	International Study of Asthma and Allergies in Childhood
ISP	Internet Service Provider
IT	Information Technology
IVF	In Vitro Fertilization
LRBCS	Liverpool Respiratory Birth Cohort Study
LRSQ	Liverpool Respiratory Symptom Questionnaire
LWH	Liverpool Women's Hospital
MAAS	Manchester Asthma and Allergy Study
MCS	Millennium Cohort Study
MPhil	Master of Philosophy
MRHS	Merseyside Respiratory Health Surveys
NCDS	National Child Development Study 1958
NHS	National Health Service
NICE	National Institute of Clinical Excellence
NIHR	National Institute of Health Research
NSHD	National Survey for Health and Development 1946

NWSHA	North West Strategic Health Area
ONS	Office for National Statistics
PAYG	Pay as you go
PPI	Public and Patient Involvement
QR	Quick Response
RSV	Respiratory Syncytial Virus
SHA	Strategic Health Authority
SMS	Short Message Service
SPSS	Statistical Package for the Social Sciences
SSN	SelectSurvey.NET
TCR	Tucson Children's Respiratory Study
UK	United Kingdom
URL	Uniform Resource Locator
WHO	World Health Organization
WWW	World Wide Web

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Chapter 1

Introduction

1.1 The Liverpool Respiratory Birth Cohort Study

The Liverpool Respiratory Birth Cohort Study (LRBCS) is a prospective, longitudinal birth cohort study that uses the self-administered Liverpool Respiratory Symptom Questionnaire (LRSQ) to conduct a biannual assessment of the respiratory symptoms experienced by preschool children in Liverpool from birth to the age of 5.⁽¹⁾ The LRSQ uses a number of domains to describe the prevalence of commonly occurring respiratory symptoms, including cough and wheeze, but is unique as it also explores the impact of such symptoms upon family function and quality of life. Table 1.1 summarises the outcome measures of the LRSQ in detail. The LRSQ will be used alongside an exposures and demographics questionnaire, that explores socioeconomic and sociodemographic risk factors for respiratory disease, such as deprivation, parental cigarette smoking, breast feeding and overcrowded housing, as well as any relevant past medical history, such as prematurity or chronic illness. This allows researchers to examine the prevalence and natural history of respiratory symptoms within preschool children living in Liverpool.

It is this assessment of both the prevalence and impact of such symptoms on this specific population and their parents that make the LRBCS a unique and valuable study. There have been several international studies that have used questionnaires to assess respiratory symptoms and their impact in adults⁽²⁻⁴⁾ and furthermore, there have been birth cohort studies in the United Kingdom that have contained respiratory elements.^(5, 6) Although some adult questionnaires explore the impact of these symptoms upon quality of life, as yet, no study has described the impact of respiratory illness in a preschool population. This study will be the first birth cohort study to do so and will use the aforementioned LRSQ.

Table 1.1 Outcome Measures of the Liverpool Respiratory Symptom Questionnaire

Domain	Respiratory symptoms in last 3 months	Questions
1	Daytime symptoms	Wheezing
2	Night-time symptoms	Cough
3	Number of colds, symptoms during colds	Rattly chest Dyspnoea
4	Intermittent symptoms	
5	During Activity	
6	Other symptoms	Noisy breathing not from chest, tachypnoea, noisy breathing from back of throat.
7	Effect on child	Feeding, waking, reducing activity, caused tiredness
8	Effect on Family	Limited activities, adjustment to family life, disturbed sleep and worry.

Mothers will be recruited to the study shortly after the birth of their child, and will complete the questionnaire, either online or by post, twice a year, commencing when their child reaches four months of age. The questionnaire has previously been validated for use in a paediatric context, however this study will provide the opportunity for researchers to further validate the eight domains of the questionnaire upon a larger sample of children. The LRBCS will be the first study to use the LRSQ longitudinally.^(1, 7) Responses from mothers will be linked longitudinally in a database to allow researchers to gain insight in to how respiratory symptoms change over time in individuals. It will also to permit researchers to investigate the changes in the patterns and prevalence of respiratory symptoms within the Liverpool preschool population over a period of five years.

Univariate and multivariate analyses will be performed using linear regression analysis to compare LRSQ scores with presence of exposures for respiratory disease. Structural equation analysis and multinomial regression analysis may also be used to assess any relationships found between these exposures and respiratory symptoms in our preschool cohort. Further validation of the LRSQ will also be performed by calculating Cronbach's alpha coefficients for the questionnaire, and the modified questionnaire using demographics and exposures will also be validated.

There are a number of factors that make Liverpool a desirable location to conduct a birth cohort study. It is of significance that the city has been recognised as being one of the most socioeconomically deprived cities in England, with high rates of cigarette smoking and associated respiratory illnesses.⁽⁸⁾ Children domiciled in the city are at higher risk of hospital admissions for bronchiolitis and are more susceptible to wheezing disorders than children

living in other parts of England.⁽⁹⁾ Furthermore, due to Liverpool's present and past industrial activity, it has been hypothesized that some of the city's districts may be exposed to significant levels of airborne dust pollution. Previous studies have demonstrated a correlation between these geographical areas and an increased prevalence of asthma and other respiratory symptoms.^(10, 11) The pre-existing knowledge about the prevalence of respiratory disease in the residents of Liverpool permits for reliable studies into the effects of these exposures, thus making Liverpool an ideal location for a birth cohort study. Approximately 8,500 births occur annually at the one centre facilitating recruitment, which is the largest single site maternity hospital in Europe. This permits researchers to access the vast majority of children born in the city.

My involvement with the LRBCS commenced in July 2012, after the study protocol (see appendix 1 for study protocol, Pickles & Semple 2012) and supplementary documents including draft versions of study materials had been finalised. Ethical approval had already been granted by proportionate review in May 2012 by the East Midlands Research Ethics Committee, part of the NHS Research Authority (Reference: 12/EM/1904).

1.2 The Burden of Respiratory Disease

Population based studies that explore respiratory morbidity and symptoms are of interest to researchers because respiratory conditions represent a significant burden to healthcare services in the United Kingdom (UK).⁽¹²⁾ Respiratory conditions are estimated to cost the National Health Service (NHS) £6 billion annually, and respiratory complaints are amongst the most frequent reasons for General Practitioner(GP) consultations for both adults and children.^(13, 14) Evidence suggests that many adult respiratory outcomes may be traced to events in childhood.^(15, 16) Furthermore, two thirds of all children under 5 years visit their GP at least once a year for either acute or chronic respiratory conditions.⁽¹⁴⁾ These conditions cause significant morbidity, with diseases of the respiratory system being the most common chronic diseases in children - one in seven children suffer from a long term respiratory condition and the prevalence of wheeze in British children, at 32%, has been reported as the highest levels globally¹⁾, and may be increasing.^(14, 17,18) Research has demonstrated that wheeze and asthma in British preschool children may cost the NHS upwards of £53 million annually.⁽¹⁹⁾

In addition to the financial and social burdens of these diseases, symptoms of the respiratory system, including wheeze and shortness of breath, can be very distressing to a child and their family, and may have a negative effect upon quality of life of the child and

caregivers.⁽²⁰⁻²²⁾ The North West of England has amongst the highest levels of respiratory disorders, and the burden of disease is particularly evident in socioeconomically deprived urban areas including Manchester and Liverpool.^(8, 9, 23, 24) These cities have some of the highest incidences of infections such as bronchiolitis, and hospital admissions for asthma in England.⁽⁹⁾

Furthermore, in addition to the direct interpersonal and socioeconomic burdens of respiratory disease in children, there may be indirect negative effect upon family function. Health-related quality of life has been identified as an essential outcome measure used in various studies and health service research, appraisals and evaluations, as they provide researchers with the opportunity to adopt a holistic approach to measuring disease impact and progression, as well as identifying unanticipated functional disabilities.⁽¹⁹⁾ Some previous studies have measured the extent of specific respiratory conditions, namely Asthma and recurrent respiratory tract infections, upon children, caregivers and their families, in the context of emotional and social functioning, school absenteeism, as well as absence from employment and financial consequences for parents, and overall family function.^(19,20) By identifying the impact of disease, these issues may be identified and addressed by clinicians, thus providing the opportunity to minimise the effect of disease upon families. Obtaining information about which areas of family quality of life are greatest affected by respiratory disease can also aid parents to understand and anticipate these difficulties, and provides evidence for schools and employers to be more empathetic towards parents. Furthermore, the provision of funding and other steps to minimise these potential adverse effects may be taken by clinical commissioning groups to further support parents. These factors can be used to demonstrate the detrimental impact of respiratory disease upon quality of life of children and their caregivers, thus allowing healthcare providers to implement supportive strategies for both the affected child and their families.⁽¹⁹⁾

The severity of respiratory conditions and symptoms is highly variable. Some children may only suffer from acute symptoms, such as those experienced in the presence of infections such as Influenza Virus or Respiratory Syncytial Virus (RSV). However, some children may suffer from recurrent or chronic symptoms, which are associated with long-term diseases such as asthma, cystic fibrosis and bronchopulmonary dysplasia. Some children may also suffer from transient symptoms that remain undiagnosed, but have a detrimental effect upon quality of life.⁽²⁵⁾

Numerous studies have been conducted on regional, national and international levels to investigate the prevalence and natural history of conditions such as asthma and acute respiratory tract infections. Several environmental, biological and genetic risk factors have been implicated in predisposing a child to respiratory disease.

1.2.1 Risk Factors for Respiratory disease within Paediatric Populations

Exposures

Cigarette Smoke A causal relationship has been demonstrated between exposure to tobacco smoke and respiratory complaints in children.^(26, 27) There is a 40% increase in the risk of wheeze in the first two years of life in children born to mothers who smoke during pregnancy, but the greatest risk is associated with postnatal environmental exposure. A number of studies have demonstrated that this factor has the greatest effect on the incidence of wheeze in preschool children.^(28, 29) Furthermore, household cigarette smoking also predisposes young children to severe respiratory tract infection requiring hospitalization, and to require the highest levels of medical care.^(27, 30)

Air Pollution Several environmental pollutants have been implicated in the aetiology of respiratory symptoms in children.⁽³¹⁾ High levels of pollution have also been associated with atopic sensitization and bronchial hyperresponsivity.⁽³²⁾ Children in urban areas suffer from more acute respiratory symptoms than their rural counterparts, which is attributed to poorer air quality and higher levels of environmental pollutants in metropolitan areas.⁽³³⁾

Social Deprivation Socioeconomic status is measured by financial income, occupation, healthcare, education and access to resources. A low socioeconomic status has been identified as an independent determinant of health. It is also considered a risk factor for respiratory diseases in children, particularly infections such as bronchiolitis.⁽³⁴⁻³⁶⁾ Children aged 0-4 years are particularly susceptible to the effects of this exposure; hospital admissions are 91% higher for the most deprived children in this age group.^(27, 37) Other factors such as low birth weight, prematurity and household cigarette smoking may be confounding, as these factors are also more prevalent in the most deprived socioeconomic groups.^(38, 39)

Overcrowding The risk of respiratory disease, particularly infections may have some correlation with the number of people living within a household, and sharing a bedroom.

However, as overcrowding or shared bedrooms are circumstances that mostly occur within socioeconomically deprived households, therefore this factor may be considered confounding.⁽⁴⁰⁾

Breastfeeding Breastfeeding exclusively for the first four months of life has been demonstrated to play a protective role against respiratory pathogens.⁽⁴¹⁾ Breastfed children living in developed countries are a third less likely to be hospitalized during the first few months of life than those who are artificially fed.⁽⁴²⁾

Exposure to other children Children that have older siblings, or that attend nursery, may be at higher risk of wheezing symptoms and colds in the first two years of life. However, there is contradictory evidence as to whether this affects the incidence of asthma and other respiratory symptoms beyond the preschool period.^(43, 44)

Demographics

Prematurity Infants born at less than 37 weeks gestation are at increased risk of both short term and long term respiratory morbidity.⁽⁴⁵⁾ Premature infants are born with immature lungs that are prone to injury. These children may also receive medical interventions which may further damage lungs. Evidence suggests that this damage may persist in to childhood and beyond.^(24, 46) Children who were born prematurely are also more prone to wheezing and conditions such as asthma, which is often more severe in this population.⁽³⁹⁾

Low Birth Weight It has been established that infants that are born with a low birth weight (<2,500g) or very low birth weight (<1,500g) are at a significantly higher risk of developing chronic respiratory symptoms.⁽⁴⁷⁾ These respiratory symptoms often persist beyond infancy. These children are prone to school absenteeism and more frequent hospital admissions due to both infections and allergic conditions such as asthma, compared to their peers.⁽⁴⁸⁻⁵⁰⁾

Sex Studies that have investigated childhood asthma have found that males are more likely to suffer from asthma and wheezing during childhood than females.^(39, 43, 51) However, it has been demonstrated that males are more likely to “outgrow” their condition during adolescence, whereas females that suffer with asthma during adolescence are more likely to experience symptoms of greater severity, and for their disease to persist in to adulthood.⁽⁵²⁾

Comorbidities Children with comorbidities, including neurodisabilities, gastro-oesophageal reflux and cardiac conditions are susceptible to both acute and chronic respiratory conditions due to the impact of these pathologies upon the respiratory system.⁽⁵³⁻⁵⁵⁾ 26% of children that have asthma have at least one comorbidity, compared with 9% of non-asthmatic children.⁽⁵⁶⁾ Furthermore, children with pre-existing conditions such as asthma or cystic fibrosis are more susceptible to respiratory tract infections which can further exacerbate symptoms.⁽⁷⁾

1.3 Birth Cohort Studies

A number of studies have been conducted to investigate the impact of these risk factors upon the aetiology and natural history of respiratory symptoms within paediatric populations. Birth Cohort studies are epidemiological studies that follow the same group of people longitudinally from birth. In principle, these studies gather an abundance of information from a group of people that share a common factor, such as birth date or geographical area. Exposures are measured at a series of time points, so that changes in disease can be studied over time. By following participants for a number of years, or even a lifetime, researchers can gain insight in to the natural history and aetiology of diseases by collecting detailed information on a wide range of exposures. It allows researchers to begin to understand the relationship between extrinsic factors such as cigarettes and social deprivation, and their interaction with the pathogenesis of disease within a population.⁽⁵⁷⁾ Cohort studies also allow researchers to directly measure the incidence or risk of disease within a population.

Numerous high profile cohort studies have been conducted both at regional and national levels in the United Kingdom and internationally, including the Avon Longitudinal Study of Parents and Children, Born in Bradford and the European Study of Pregnancy and Childhood. These studies have provided a wealth of data with regards to health and social inequalities as well as the changing demographics of their populations (Table 1.2). These studies have become key sources of information for governments and other bodies to form policies and legislation.

These studies are of relevance to the Liverpool Respiratory Birth Cohort Study as they have gathered valuable data about the health of participants, and several of the questionnaires have included respiratory components in addition to sections on education, as well as clinical exposures such as cigarette smoking, diet, and social deprivation.

Researchers focused upon the strengths and limitations of previous birth cohort studies when designing the LRBCS.

A literature review was performed using reputable electronic medical research databases, using a predetermined list of keywords (see appendix 2) to identify relevant studies. The abstracts of articles were then screened to determine their relevance to this study. Articles of studies of significance were retrieved and appraised, and their reference lists were also searched to identify any studies that were not in the original search.

Study Name	Abbreviation	Country/Region	Year	Type	Number of Participants	Areas of Interest/Aims
National Survey of Health and Development ⁽⁵⁸⁾	NSHD	United Kingdom	1946	National	5,362	Outcomes of pregnancy, Ageing
National Child Development Survey ⁽⁵⁹⁾	NCDS	United Kingdom	1958	National	17,416	Obstetric and social factors leading to stillbirth or infant mortality, lifespan human development.
1970 British Cohort Study ⁽⁶⁰⁾	BCS70	United Kingdom	1970	National	16,571	Social and biological factors associated with neonatal mortality.
Millennium Cohort Study ⁽⁶¹⁾	MCS	United Kingdom	2000	National	18, 819	Determinants of health in children of the 21 st century
The Newcastle Thousand Families Birth Cohort ⁽⁶²⁾	-	Newcastle, United Kingdom	1947	Regional	1,142	Infant Mortality, Childhood Infection, Ageing.
Aberdeen Children of the 1950s study ⁽⁶³⁾	-	Aberdeen, United Kingdom	1950	Regional	12,150	Cognitive function and mental health in childhood, ageing in an urban post-war population
Avon Longitudinal Study of Parents and Children ⁽⁶⁴⁾	ALSPAC	Bristol, United Kingdom	1991	Regional	13,761	Features of the environment, genotypes and the interaction between the two that influence the health, development and well-being of children throughout the life course
Isle of Man Birth Cohort Study ⁽⁶⁵⁾	-	Isle of Man, United Kingdom	1991	Regional	1,314	Social, demographic and environmental determinants of health in Celtic people, and to compare with children across Europe.
Born in Bradford ⁽⁶⁶⁾	BiB	Bradford, United Kingdom	2007	Regional	13, 776	To study the determinants of health and disease in a bi-ethnic socially deprived population.
European Longitudinal Study of Pregnancy and Childhood ⁽⁶⁷⁾	ELSPAC	Europe	1991	International	~40,000	To compare the effects and impact of environmental and genetic factors upon the health and developments of children

						across Europe
Growing Up in Scotland ⁽⁶⁸⁾	-	Scotland, United Kingdom	2004	National	5,217	Holistic (social, genetic and environmental) approach to understanding child development in Scotland)
Steps to the Healthy Development and Well-being of Children ⁽⁶⁹⁾	STEPS	Turku, Finland	2008	Regional	1,817	The precursors and causes of problems in child health and well-being
Generation R ⁽⁷⁰⁾	-	Netherlands	2002	National	9,778	To identify normal generic and environmental factors contributing to normal or abnormal growth and child development.
All Babies in Southeast Sweden ⁽⁷¹⁾	ABIS	Sweden	1997	Regional	17,055	Nutrition, physical activity, sleep pattern, infections, psycho-social factors, stress, drugs, vaccinations, genetics upon the presence of atopy and autoimmune diseases.
National Children's Study of Environmental effects on Child Health and Development ⁽⁷²⁾	-	United States of America	2007	National	~100,000	Investigation of health and development of a large national sample of children born in the United States of America.
Dunedin Multidisciplinary Health and Development Study ⁽⁷³⁾	-	Dunedin, New Zealand	1972	Regional	1037	To study the nature and development of common health and development problems in childhood
Mater University of Queensland Study of Pregnancy and its outcomes ⁽⁷⁴⁾	MUSP	Mater, Australia	1981	Regional	7,223	Factors associated with adverse outcomes in pregnancy and childbirth, and social and environmental determinants of health, development, learning and behaviour in children and young adults.
Amsterdam Born Children and their Development ⁽⁷⁵⁾	ABCD	Amsterdam, Netherlands	2003	Regional	6,161	Association between lifestyle, psychosocial conditions, and nutritional

						status during pregnancy, and the child's health at birth, childhood and later life.
Danish National Birth Cohort ⁽⁷⁶⁾	-	Denmark	1996	National	91,256	Foetal growth and infant health as health outcomes and as a determinant of later health
Norwegian Mother and Child Birth Cohort Study ⁽⁷⁷⁾	MoBa	Norway	1997	National	64,136	To test aetiological hypotheses by estimating the association between exposures and diseases.
Pelotas Birth Cohort Studies ⁽⁷⁸⁻⁸⁰⁾	-	Pelotas, Brazil	1982, 1993, 2004	Regional	5,914 5,265, 4,262	A series of three cohorts of children conducted in the same urban area of Brazil to examine the changing health of the population.

*Table 1.2
Longitudi
nal
Studies
of
Children*

1.3.1 The National British Birth Cohort Studies

National Survey of Health and Development

The United Kingdom has a long tradition of conducting longitudinal studies, which started with The National Survey of Health and Development (NSHD). Established in March 1946, the study continues to gather valuable data from 3000 of the original 5362 participants, 67 years later.⁽⁸¹⁾ Initially, the study aimed to appraise the costs of pregnancy and childbirth to the newly formed National Health Service (NHS).⁽⁸²⁾ A further aim of NSHD was to describe health and survival in relation to home and socioeconomic circumstances, allowing researchers to explore the precursors of poor health and disease.⁽⁸³⁾ It is admirable that the study has maintained impressive response rates throughout, which is partially attributed to the excellent relationship maintained between researchers and participants. The study is now being linked with several other cohort studies to investigate the effects of ageing.⁽⁵⁷⁾

Despite being focused upon the health and development of the child as a whole, the NSHD did have a respiratory component. Researchers were able to describe links between exposures and risk factors such as lower respiratory tract infections, low birth weight and crowded living circumstances in preschool children, with reduced peak expiratory flow scores and increased risk of chronic obstructive pulmonary disease (COPD) in later life. However, parental tobacco smoking (and thus exposure during childhood) was only recorded retrospectively, as the significance of such exposures were not initially realised within the medical profession. Therefore, conclusions about this particular exposure may be subject to recall bias.

As a cohort study, the significance of the NSHD is undeniable. It is the longest running birth cohort study in the world, which has gathered a wealth of unique information about its participants, and it has demonstrated the complex interactions between genetics, social demographics, health and the normal ageing process. The study's co-ordinators make contact with the cohort annually with a birthday card and a review of recent findings from the study, and provide the opportunity for participants to notify them about any changes in address or circumstances. Efforts to continuously involve participants have been a fundamental part of the study's impressive response rates.

The main limitation of the study is recruitment. The study initially followed children born within one week in 1946 using data from Health Authority Databases. Due to the narrow recruitment frame, the sample not to be representative of the population as a whole due to the effects of seasonality upon trends in health. It must also be considered that this cohort only consisted of children born to married mothers, which introduced bias

to the selection of infants, and ultimately may result in certain population groups being underrepresented in the study.

Similarly to other cohorts, funding has limited the scope of the NSHD throughout the study. As a result of these financial issues, co-ordination and control of the study has changed between numerous parties with different priorities and research aims. This lack of continuity may have hindered the results of the study. However it is difficult to overcome these financial and management obstacles due to the longitudinal nature of birth cohort studies.

National Child Development Survey

Following the success of the NSHD, another longitudinal study, the National Child Development Study (NCDS), was launched in 1958. The study follows a larger cohort of around 17,000 individuals, whom again, were born within a single week in 1958. Similarly to the NSHD, the study was initially commissioned to investigate maternal and neonatal health in the UK. The initial data from this cohort evoked the debate that ultimately resulted in the wider availability of easily accessible maternity services in hospitals. The study eventually grew to cover a broad scope of health related issues as it followed cohort members longitudinally in the transitions from childhood to adolescence and adulthood.⁽⁵⁹⁾

Like the NSHD, the NCDS also investigated respiratory disease in its participants. The study used a questionnaire that enquired about a variety of symptoms during “sweeps” of the cohort, which included domains to explore symptoms and diagnoses of a respiratory nature such as “asthma, wheezy bronchitis and pneumonia” at ages 7, 11, 16, 23 and 45 years old.⁽⁸⁴⁾ Two thirds of the cohort that had wheeze at age 16 had initially developed respiratory symptoms before age five. A quarter of the children with a history of asthma or wheezy bronchitis by 7 years old reported still experiencing wheeze at 33 years. This data suggests that respiratory disease may be life-lifelong diagnoses, which often develop in the preschool years and persist in to adulthood. Researchers also found that other factors, such as financial adversity in early life could also have a negative effect upon respiratory health in later life, which is consistent with the findings of the earlier 1946 cohort.^(58, 85)

1970 British Birth Cohort Study

The 1970 British Birth Cohort Study (BCS70) is another on-going multidisciplinary longitudinal study of children born in the UK. The study takes as its subjects all individuals born in England, Scotland and Wales within a particular week of 1970.⁽⁶⁰⁾ The structure and context of this cohort study is similar to the previously discussed studies, in that it investigates family circumstances, health, education and social development at specific

intervals throughout the lives of the cohort members. This permits the datasets from all cohorts to be compared, which allows researchers to gain insight in to the changing trends in the health of the British population across a number of generations. Furthermore, data can help researchers create new hypotheses with regards to the natural history and aetiology of some diseases. The Centre for Longitudinal Studies (CLS) co-ordinates all the national British birth cohort studies. The CLS described a 70% increase in the incidence of wheeze in the 1970 cohort in comparison to the 1958 group.⁽⁸⁶⁾ However, researchers must consider that population sampling in the 1970 cohort differed slightly from the previous birth cohort studies. The study design permitted new participants, who were born within the reference week and had immigrated, to be recruited to the cohort and participate in questionnaires. This helped maintain an adequate sample size for the cohort.

A significant limitation in the study's method was its dependence upon the educational system to follow up participants. Tracing individuals became increasingly difficult and expensive once participants had reached school leaving age, resulting in non-response of 48% of participants in the first sweep that occurred after the cohort had left education.⁽⁶⁰⁾ A strength of the BCS70 was the multidisciplinary approach of its study design: an initial aim of the study was to identify the effects of socio-economic status upon infant health and development.

A significant amount of data has been collected from the cohort with regards to cigarette smoke exposure and respiratory wellbeing from infancy to adulthood. Researchers discovered that maternal cigarette smoking increased the risk of hospital admissions for severe lower respiratory tract infections in children under the age of five years.⁽⁸⁷⁾ Furthermore, the prevalence of wheeze was also increased in the cohort children preschool children of smoking mothers.⁽⁸⁸⁾ Therefore, despite its difficulties and restrictions, the BCS70 successfully identified the effect and impact of socio-economic factors upon all aspects of a child's health and well-being. The study clearly demonstrated that an association exists between maternal cigarette smoking and exposures with respiratory disease in paediatric populations.

Millennium Cohort Study

The most recent of the national cohort studies conducted in the United Kingdom is the Millennium Cohort Study (MCS), which is following the lives of around 18,819 children born in Great Britain between the years 2000-2001.⁽⁸⁹⁾ The first interviews with parents were conducted when their child reached 9 months of age. This structured interview largely focused upon pregnancy and birth of the child. Further sweeps of the cohort were

conducted in 2005, 2006, 2008 and 2012. Recruitment and sampling methods differ from the other British birth cohort studies. This is the first of these studies to include children born in Northern Ireland.⁽⁶¹⁾ The initial MCS survey covered a number of domains, including household structure, ethnicity, parents and family members, income, health and development. From a respiratory and health perspective, there has been less data available from the MCS than the previously discussed birth cohort studies. This may be attributed to the design of the study, as it places a greater emphasis upon social rather than medical factors upon development and wellbeing.

However, researchers did observe that respiratory tract infections and wheeze were the two most frequently occurring health problems for which children enrolled in the study were taken to their GP or to an accident and emergency department during infancy. A quarter of all hospital admissions for the cohort during the first 9 months of life were due to pneumonia or other infections of the respiratory tract.⁽⁹⁰⁾ Researchers also found that children that were breast fed were less likely to require medical attention and hospital admissions for respiratory tract infections.⁽⁴¹⁾ This supports the evidence from other birth cohort studies of the protective effects of breast feeding upon clinical outcomes including atopy and respiratory diseases in childhood.⁽⁹¹⁾ Results from the MCS also demonstrated that children who were born as the result of assisted reproduction therapies, such as In Vitro Fertilization (IVF), were more likely to suffer from respiratory disease in childhood.⁽⁹²⁾

The MCS used the strengths and limitations of previous birth cohort studies conducted in the UK to create a robust study design. The study helped evaluate national initiatives aimed at narrowing the social gap such as Sure Start and Child Trust Fund. The data collected by the study is being monitored by the UK Government's advisory programme, Foresight. This programme helps plan for the future needs of the British population in a variety of disciplines, and it is hoped that MCS data will help shape changes in legislation and policy to reflect the changing demographics of the country.

Impact of the National British Birth Cohort Studies

The results from the four national British Birth Cohort Studies have been recognised as a valuable source of information about health trends within the UK population. Subjects were sampled from national UK population, which permits results to be generalised to a greater extent than regional cohort studies. This has resulted in the UK government utilizing the results from these studies to gain insight in to the needs of the British population, and consequentially to form policies and legislation that reflect these needs. Results from these

studies have been incorporated in numerous reports, which include the Plowden Report into Primary Education (1967), the Finer Committee Report on One Parent Families (1966-74), the Warnock Committee on Children with Special Educational Needs (1978), the Independent Inquiry into Inequalities in Health (1998), the Moser Committee on Adult Basic Skills (1997-99), The Marmot Review into health inequalities in England (2010), and the report from the National Equality Panel (2010).

1.3.2 Regional British Birth Cohort Studies

Despite the information from the National British Birth Cohort Studies being invaluable for researchers and clinicians alike, some questions remain unanswered. The broad intervals of time between “sweeps” make it difficult to collect large amounts of data retrospectively without introducing recall bias. Some of the smaller, regional British Birth Cohort Studies were able to minimize this bias by performing more regular sweeps.

Avon Longitudinal Study of Parents and Children

In 1991, the Avon Longitudinal Study of Pregnancy and Children (ALSPAC), or “the Children of the 90’s”, was launched by the University of Bristol. In contrast to the aforementioned cohorts, ALSPAC recruited children from one region, Avon, in the south West of England, over a one year period of from 1991-1992. The study follows the development of participants from early pregnancy to adulthood, whilst longitudinally linking information from parent- and child-completed questionnaires with routine hospital data and with biological samples and other health information. Social and educational development were also studied in order to gain a comprehensive insight in to the lives of the individuals participating in the study.^(5, 93) The study was part of the European Longitudinal Study of Pregnancy and Children (ELSPAC), which was initially intended as *“a prospective geographically based series of population studies...designed to start in pregnancy and to follow the cohort of birth until age 7 years”* according to the original protocol published by the research group in 1989.⁽⁹⁴⁾ ELSPAC is further discussed in the international cohort study section.

Researchers successfully enrolled around 75% of eligible pregnant women to the study, and a wealth of data has been gathered since the study commenced recruitment in the early 1990s. To date, members of the Avon cohort have completed almost 60 cross-sectional questionnaires, from as early as the eighth gestational week of pregnancy up until early adulthood. Supplementary data has also been extracted from hospital records, and participants have also had nine clinical assessments with research nurses and physicians, the first of which occurred at age seven.⁽⁶⁴⁾

Attrition rates have so far remained minimal in comparison with other cohorts. However, they may now begin to be affected by the transition of the cohort in to adulthood. A trend of decreasing response rates was first detected during the cohort's adolescent years. Other birth cohort studies have found this to be a difficult period for researchers in terms of participant retention. However, the decision of the research team to incorporate new online versions of questionnaire in to the study design may aid the retention of participants. These online questionnaires may also lessen the limitations associated with traceability that have been reported by other birth cohort studies.⁽⁶⁰⁾ A key strength of the study is that it was always intended to be a birth cohort; thus researchers were able to organize ongoing financial support for the study. As a consequence, ALSPAC has always been well funded which has aided in the study's retention.

There have been several hundred publications by the study's research team. A key paper outlining the all the significant results was published J Golding, the director of ALSPAC, in 2010.⁽⁹⁵⁾ From a respiratory perspective, key discoveries included evidence to support that further confirms the relationship between maternal cigarette smoking during pregnancy and the risk of wheeze in infants and young children.⁽⁹⁶⁻⁹⁸⁾ Researchers were also able to associate the prevalence of atopy with to excessive levels of domestic hygiene, as well as a positive family history of asthma, hay fever or eczema.⁽⁹⁷⁾ The study also provides strong evidence that a relationship exists between environmental factors and respiratory health.⁽⁹⁹⁾ Individuals may be predisposed to wheeze and respiratory symptoms prenatally or during infancy, but that many children "outgrow" these symptoms in late childhood and adolescence.

Isle of Man Birth Cohort Study

Another branch of ELSPAC was the Isle of Man birth cohort study. Like ALSPAC, the study commenced enrolment of pregnant women domiciled on the island in 1990. Recruitment was inclusive; the study aimed to recruit all infants born to the 75,000 inhabitants of the island within a specified period between 1991-2. Researchers reported that adopting a "personal" approach to recruitment, by involving research midwives, to be the most effective method of recruitment to the study. The Isle of Man cohort had retained 85% of the original 1314 participants by age 15 years. The main loss was emigration. Researchers attempted to minimize the limiting effects of this factor by inviting immigrants that were born within the eligible timeframe to be enrolled. This helped reduce the effects of migration upon the size of the cohort and ultimately the statistical power of the study.

Questionnaires were sent to parents of participants in ten sweeps. The first sweep occurred prenatally, and the final questionnaire was sent at age 15/16. Further data about participants was obtained from hospital records and other routine data sources. Like the ALSPAC cohort, teachers were also asked to complete questionnaires about the children. Additionally, children were invited to an assessment with the research team at age seven years, when both cognitive ability and physical health were evaluated, and biological samples were obtained and analysed.

The recruitment rate and retention within this cohort is unprecedented at approximately 99% of eligible mothers being initially recruited, and response rates were mostly maintained throughout. Another fundamental strength of this study is its significance as part of a larger study. The association and similarity in study design and sampling methods with the Avon cohort and the international ELSPAC cohort permit researchers to efficiently and reliably contrast data sets from the Isle of Man with samples with similar demographics both locally and from other geographical areas, both British and European. It permits the analysis of results of the individual island cohort, and within the setting of a larger cohort of children. The island was selected for a population based birth cohort study as it has a unique population that consists almost equally of the indigenous Manx population and immigrants. This allows researchers to reliably contrast the possible effects of genetics and environment upon these distinct population groups.⁽⁶⁵⁾

Although these unique attributes of the Isle of Man cohort make the island an interesting setting for a population-based birth cohort study, Goodfellow proceeds to explain that due to funding issues a large quantity of the data collected from the study has yet to be analysed. Attempts were made by the research team to minimise the effects of migration upon the cohort size, it must be acknowledged that it may limit the ability to longitudinally link data and to gain a true insight in to the development of children, which is a key advantage of the design of a cohort study.

Born in Bradford

Bradford, a city in the north of England, is considered to be amongst the country's most socioeconomically deprived areas.⁽¹⁰⁰⁾ The city's unique, bi-ethnic, population mainly comprises of people from either White British (50%) or Pakistani (44%) origin, resulting in the city being considered one of the most ethnically diverse cities in the UK. For these reasons, researchers decided it would be an ideal location for a birth cohort study that would investigate the roles of environment and genetics upon health, and to examine any differences between the two genetically distinct populations.⁽¹⁰⁰⁾

The study recruited over 13,000 mothers at Bradford Royal Infirmary between March 2007 and November 2011 during various prenatal appointments, or during their perinatal hospital admission. Over 80% of eligible pregnant women domiciled within the study agreed to participate. The study uses a combination of routine data, such as hospital and general practice records, alongside data collected from biological samples (including cord blood, urine and blood samples), as well as physical examinations and parental-completed questionnaires. Within the main cohort, there are also two nested studies: ALL IN, a study about allergies and infections, and BiB 1000, which studies weight gain and obesity. Researchers hope that the wealth of data available about its participants will allow them to comprehensively profile the population of the city.⁽⁶⁶⁾

By age four years, mothers had completed seven questionnaires, and there had also been three partner-completed questionnaires. This study is still considered to be in its early stages, thus there is little longitudinal data currently available from the study. From a respiratory perspective, to date, there have been no publications that explore respiratory morbidity specifically within the cohort, however participants have been part of a larger European study that investigates the development of allergy in children, which includes asthma and allergic rhinitis.⁽¹⁰¹⁾

Researchers report a low attrition rate, which, like the Isle of Man birth cohort study, they attribute to upholding an excellent relationship with participants. Researchers organise regular community events to engage participants, and use the media to raise the profile of the study. To further enhance participation and response rates, which were around 30% during the study's pilot phase, researchers used alternative methods for follow up of participants. These strategies included the use of multi-lingual interviewers that were employed to facilitate the participation of parents that were unable to read or speak English, which maximised the study's participation capacity. Profiling of the cohort has demonstrated participants as being a representative sample of the city's population, which demonstrates that there was minimal selection bias, and that the extra measures taken to reduce the effects of poverty, language barriers and other cultural differences have been successful. A limitation of the study, due to the unique demographics of the Bradford population, is that many of the findings cannot be used to make inferences about the wider UK population, and it also makes it difficult to compare results with other cohorts.

1.3.3 International Birth Cohort Studies

ELSPAC

The European Longitudinal Study of Pregnancy and Childhood (ELSPAC) is a large longitudinal study that was promoted by the World Health Organization in the late 1980s, and co-ordinated by the ALSPAC team at Bristol University.⁽²⁹⁾ The study consisted of a series of population based cohort studies set in various cities in Europe, with participating countries including the United Kingdom (the aforementioned Isle of Man and Avon cohorts), Czech Republic, Ukraine, Slovakia, Russia, Croatia, Estonia, Greece and Spain. Specific regions within participating countries were chosen, with focus on encompassing both urban and rural areas. The main research tools used in the study are standardized questionnaires that are distributed to both parents, the child, teachers and health care professionals. Although some participating regions incorporated additional investigations, examinations and questionnaires, the baseline protocol remained the same, which permits the data collected from over 40,000 international participants to easily be compared, contrasted and meta-analysed.

This study has the potential to have great impact upon health policy in Europe as a whole, however the impact has, so far, been smaller than hoped. Despite participating countries releasing data from their own cohorts, little information is available about ELSPAC as a whole. Some countries, such as the Czech Republic and the UK remain active. Several of the original countries, including Greece and Spain, have now abandoned the project, which was attributed to funding issues and the economic downturn.

The ELSPAC questionnaires have looked at respiratory symptoms and the effects of tobacco exposure.⁽²⁹⁾ Cigarette smoking was more prevalent amongst the British cohort, and an analysis of the nature of wheeze within two of the populations involved with ELSPAC demonstrated that parental, and particularly maternal cigarette smoking was associated with wheeze in young children. Furthermore, abnormal lung function was present in the children of cigarette smokers shortly after birth, when environmental exposures could not have been apparent.⁽²⁹⁾

1.3.4 Respiratory Birth Cohort Studies

The significance of the previously discussed results demonstrate the power of birth cohort studies to provide a valuable research platform for investigating modern research questions and evaluating both general and specific areas of health and wellbeing. From a respiratory perspective, studying the prevalence and nature of respiratory symptoms from birth allows researchers to assess the interactions between environmental and genetic factors as they

occur. Data can be very reliable due to the short periods of participant recall in this study design. Many studies have demonstrated that early life health may have significant impact upon morbidity in later life.

Despite the benefits of the holistic approach adopted by the aforementioned cohort studies, which gather a variety of data about the child's life as a whole, studies that specifically investigate respiratory morbidity within paediatric populations are also advantageous. These studies can reveal trends in the effects of specific exposures or protective factors, such as tobacco smoke and breastfeeding, upon the prevalence of symptoms, and explore the symptoms in greater depth than general cohort studies. Some paediatric studies have investigated the aetiology of particular disease processes in children, such as asthma and allergies such as rhinitis, whereas other studies focus more upon symptoms, than doctor diagnosed conditions such as wheeze and other breathing difficulties.

Tucson Children's Respiratory Study

The Tucson Children's Respiratory Study (TCRS) is an American birth cohort study that commenced in 1980.⁽¹⁰²⁾ It was the first respiratory birth cohort study, and it aimed to collect extensive data about the respiratory health of its 1246 participants from birth to adulthood, in order to determine risk factors for respiratory infection in childhood and the development of chronic obstructive airway diseases in adulthood.⁽¹⁰³⁾ The study aimed to recruit all healthy newborn infants being cared for by one American Health Maintenance Organization (HMO) over a four and a half year period, and information was collected from self-administered questionnaires, interviews, biological specimens, and routine data.

Significant findings from Tucson include describing that wheeze is a heterogeneous symptom with numerous phenotypes that are expressed differently at the various stages of childhood, and is not necessarily a feature of asthma.⁽¹⁰²⁾ Researchers were able to identify a number of risk factors and the role of infection in the aetiology of childhood wheeze.⁽¹⁰⁴⁾ Wheezing syndromes during preschool years may be transient and limited to these years only, or persistent, where symptoms continue to be present in adolescence. Children who were to become persistent wheezers later in childhood were able to be identified during their first wheezing episodes due to alterations in their immune responses.⁽¹⁰⁵⁾ Researchers also found that children with low respiratory function at birth were likely to have persistently poorer function throughout childhood, and that these children were more susceptible to respiratory tract infections.⁽¹⁰²⁾ Data from the study has been successfully used to create an asthma indicative index, which uses clinical parameters to indicate the

risk of a wheezing preschool child becoming asthmatic later in childhood.^(106, 107) However, despite efforts to validate this tool in other cohorts, there has been some controversy with regards to the validity of the tool in clinical practice.^(108,109, 110)

The Manchester Asthma and Allergy Study

The Manchester Asthma and Allergy Study (MAAS) was established in 1995 with the aim to study the natural history of asthma and other atopic conditions within an unselected population birth cohort. Researchers focused upon two main risk factors: family history and the presence of known allergens within the child's home environment.⁽¹²⁾ The study enrolled approximately 1000 participants during the antenatal "booking" visits (8-10 weeks gestation) over a period of 1.5 years. At enrolment, parents were screened for allergies and the children were allocated a risk group in accordance to results, and there was a nested intervention study in the high risk group which included a strict allergen avoidance regimen during pregnancy and the first year of life.⁽¹¹¹⁾ This permitted researchers to gain significant information regarding genetics, but this data was also utilized in a nested study that analysed allergy and atopy within the adult population of in addition to the paediatric cohort.⁽¹¹²⁾ Children attended assessments at ages 1, 3, 5, 8 and 11 years of age. Parents completed the previously validated self-administered ISAAC questionnaires about their children, and biological samples and lung function testing was also undertaken.

Results from MAAS provide further evidence that maternal cigarette smoking during pregnancy significantly increased the likelihood of childhood wheeze.⁽¹¹³⁾ Children that had a personal history of wheeze, and children of atopic parents, with or without a personal history of atopy, were all found to have poorer lung function at age three years.⁽¹¹⁴⁾ Researchers involved with MAAS state that wheeze is a clinical symptom that is almost always associated with pathology, and is never a feature of a normally functioning respiratory system. Other symptoms, such as cough, may also be features of underlying pathology. However, wheeze may also be normal feature in the context of acute infections.⁽¹¹⁵⁾ The prevention study nested within MAAS demonstrated a lower incidence of respiratory symptoms in children at high-risk of such symptoms when the home environment was manipulated to minimize the likelihood of allergic sensitization.⁽¹¹⁶⁾ Similar studies have had contrasting results thus further investigation is required.^(117, 118)

1.3.5 Review of Birth Cohort Study Design

Birth Cohort studies are observational studies that follow a defined population over a period of time. The risk factors and health outcomes of subjects may be monitored continuously, or they may be assessed repeatedly at specified time intervals. Therefore, as observational studies, they do not involve any experiments or any other interventions by researchers. The primary purpose of these studies is to identify and examine the relationship between suspected or known risk factors or exposures with the prevalence of disease as an outcome. This permits hypotheses about these risk factors, such as cigarette smoke exposure, to be tested by comparing the prevalence or incidence of disease in various groups that are identified as being in different levels of risk for disease. Prospective birth cohort studies are amongst the strongest observational study designs; they supersede case-control studies or case series as they facilitate the collection of complete data sets, and are subject to minimal recall bias in comparison to retrospective studies. One of the greatest benefits of the study design is that the data permits researchers to calculate relative risks of individual or cumulative factors, and gain insight in to the aetiology of disease processes. However, there are limitations of this study design. In order to obtain sufficient data, it is necessary to study large number of individuals over an extended period of time. The prolonged period of follow-up involved in this study design accounts for the larger attrition rates associated with this study design. Loss to follow-up may result in incomplete data sets this limiting the statistical power of the study. This is why a large numbers participants is required by researchers wishing to conduct research using this study design. It also usually requires considerable logistical effort to co-ordinate recruitment and subsequent follow up of participants. It may be frustrating for the researchers involved, as these studies may not yield significant results for a number of years. These reasons demonstrate why it is necessary for investigators to have sufficient evidence for their hypotheses prior to commencing a birth cohort study. Despite the efforts required to conduct these studies, to date, there have been a number of birth cohort studies that have demonstrated results that justify the effort required.⁵

1.4 Other Significant Paediatric Studies with Respiratory Focus

International Study of Asthma and Allergies in Childhood

The largest study of this type to date is the International Study of Asthma and Allergies in Childhood (ISAAC). This is an international study that was established in 1991 to investigate the natural history of atopic disease such as asthma, eczema and allergic rhinitis.⁽¹¹⁹⁾ The study has become the largest worldwide collaborative research project. To date, it has

involved two million children in 105 countries. The methods are consistent in each of the 306 centres involved with the study, which provides researchers to easily compare results for the whole cohort, and to detect significant differences.

The study has so far consisted of three phases. The first involved a written questionnaire that was administered for two age groups: children aged 6-7 years, who had a parent completed questionnaire, and adolescents aged 13-14 years who completed a self-administered questionnaire.⁽¹²⁰⁾ The second phase involved assessment of lifestyle and environment, and in-depth clinical analysis including treatment, symptoms and the third phase was a repeat of phase one after five years had elapsed.^(120, 121) The first phase of the study described the large variation of the prevalence and severity of asthma and other allergic conditions between participating countries. Centres in developed countries, including the United Kingdom and Ireland, Australia, New Zealand, and America reported the highest prevalence of asthma, and significantly, they also found that children of similar genetic origin domiciled in different geographical areas or countries had very different phenotypes, which suggests environment contributes significantly to the aetiology of these diseases.⁽¹²¹⁾ The overall prevalence of atopic disease including asthma were also found to have increased in many centres during the third phase, however this was less pronounced in high prevalence areas.⁽¹²⁰⁾ Results from British centres described significant associations between passive smoking and the incidence of respiratory symptoms during childhood, as well as other factors such as the presence of household increasing the risk of wheeze and rhinitis, and emissions from certain fuels used within the household also having adverse effects upon respiratory symptoms.⁽¹²²⁾

Due to the worldwide impact of the study, fourth and fifth phases are currently being designed and incorporated in to the study design. The study has successfully demonstrated that environmental factors are key in the development of respiratory symptoms worldwide.⁽¹²³⁾ The study has been commended the study for its improvements to the engagement of researchers from developing countries and the World Health Organization and World Allergy Association actively encourage the use of the ISAAC data in policy making.^(124,125)

The Leicester Respiratory Cohorts

The Leicester Respiratory cohorts consist of two stratified random samples of children domiciled within the Leicester Health Authority Area in England.⁽⁶⁾ The initial cohort, established in 1990, included a community based sample of 1650 children born in the area between 1985-1990, and described the prevalence and aetiology of doctor diagnosed

asthma, recurrent cough and other wheezing disorders, chronic rhinitis and habitual snoring in children aged 0-5 years living in Leicestershire.⁽¹²⁶⁾ The success of the initial cohort resulted in a second cohort of approximately 8700 children aged 1-4 years being established in 1998. The study collected demographic data as well as information about growth, immunizations, and other health related events in childhood as well as exposures including breastfeeding and family history of asthma and atopy. The area in which the study is conducted has a multi-ethnic population, which allowed researchers to understand the relationship between genetics and environment upon the presence of respiratory disease. To determine the impact of deprivation upon the prevalence of respiratory symptoms, complete postcodes for all the address at which participants had been resident were assigned Townsend deprivation index scores.

Researchers from Leicester also collaborated with the research team from the aforementioned Tucson birth cohort study. The data from Leicester supports evidence from Tucson that there are various mechanisms that lead to childhood wheeze, and that allergen-induced and infection-induced wheeze should be considered two distinct disorders with independent mechanisms.^(102, 115, 127, 128) The Leicester cohort was also used to attempt to further validate the controversial Asthma Predictive Index from Tucson, and despite discovering that the tool itself had no significant advantage over simple clinical appraisal of the pattern of symptoms, researchers were able to conclude that the pattern of wheeze and other respiratory symptoms in infants and preschool children are a key factor in predicting which children were likely to become asthmatic.⁽¹⁰⁸⁾ Researchers were also able to demonstrate the significance of environmental risk factors during early life in the aetiology of asthma, by demonstrating similar a prevalence of wheeze in children of southern Asian origin and white British children, despite the prevalence of wheeze traditionally being low in southern Asian countries.^(129, 130) The study was also amongst the first to investigate the economic and social impact of respiratory disease in preschool children.⁽²²⁾

When considering the significance of the results from this study, it is disappointing that children were not enrolled until they were one year old. This has limited the availability of data about exposures during pregnancy and early infancy, which may have a contributing role in the aetiology of wheeze, and although data was collected retrospectively, it may be subject to recall bias.⁽⁶⁾

Global Asthma and Allergy Excellence Network

In 2004 the Global Asthma and Allergy Excellence Network (GA²LEN) was established with the aims of uniting research and existing knowledge of asthma and allergies in children across the European Union.⁽¹³¹⁾ This was to be achieved by pooling data from a number of European longitudinal studies of children, and the project aimed to compare study designs including recruitment methods and contrast exposures or outcome measures for respiratory or allergic disease in birth cohorts conducted in Europe to create a database that may address previously unanswered research questions by providing a large enough samples for meta-analyses with sufficient statistical power. The database includes information from 25 European studies conducted in 10 countries that focus on respiratory disease, allergy and atopy. Researchers found that many studies had used questionnaires from the ISAAC study, signifying a homogenous definition of Asthma across a number of studies which is particularly useful for comparison and analysis.⁽¹³¹⁾

1.3.5 Studies about respiratory symptoms in Merseyside

There is an increased prevalence of respiratory disease in both the adult and paediatric populations in Merseyside.⁽⁹⁾ Poor health outcomes in the city may be partially attributed to the severity of socioeconomic deprivation in the city, with over 75% of the city's residents being considered as deprived with approximately a third of children under 16 years of age living in relative poverty.⁽¹³²⁾ Birth weights are also lower than the English national average, as is the number of children who are breastfed, despite the presence of well-funded local health promotion initiatives, and cigarette smoke exposure is also a significant health problem.⁽¹³³⁾

Some of the effects of these exposures upon the children living in the city have been investigated to an extent within school-age children living in Liverpool and surrounding areas by the Merseyside Respiratory Health Surveys (MRHS). These surveys were a series of four cross-sectional studies of children aged 5-11 years in Merseyside that were conducted in 1991, 1993, 1998 and 2006.⁽¹³³⁾ The studies investigate childhood health outcomes, primarily asthma and obesity, in relation to risk factors including smoking during pregnancy, passive exposure to cigarette smoke, residential location and socioeconomic deprivation.⁽¹³⁴⁻¹³⁶⁾ The main outcome measures were doctor-diagnosed Asthma (DDA) and the presence of three specific respiratory symptoms: wheeze, shortness of breath and cough. Parent-completed questionnaires were administered to appraise the respiratory health of a total of 6,577 schoolchildren living within socioeconomically deprived areas of Merseyside.⁽¹³⁶⁾

The studies found that there was a relationship between particular patterns of respiratory symptoms, such as cough alone related to specific risk factors, such as living in areas with high levels of environmental pollution. It also found that the presence of dyspnoea, cough and wheeze together were indicative of allergic disease, regardless of the geographical location of the child's residence or school.⁽¹³⁵⁾ The studies demonstrated the significance of environmental factors in the aetiology of respiratory morbidity in the city, with children domiciled within 2 kilometres of the city's industrial docklands having a significantly higher prevalence of respiratory symptoms, which is attributed to high levels of dust deposition in the area.⁽¹⁰⁾ Approximately a third of parents reported that their child had been diagnosed with asthma, and 11% of children had a history of at least one hospital admission for a condition of the respiratory tract.⁽¹³⁷⁾ The prevalence of DDA was found to be significantly higher in children from a lower socioeconomic background.⁽³⁸⁾ This suggests that a relationship exists between deprivation and poor respiratory health in children living in Merseyside. Researchers estimated that almost half of children enrolled in the study were regularly exposed to environmental tobacco smoke, which may also account for the increased prevalence of respiratory disease in the area.^(134, 137)

The MRHS also detected a high prevalence of maternal smoking during pregnancy in Merseyside, particularly amongst teenage mothers.^(138, 139) In 1998 and 2006, 38% and 27% of mothers reported smoking during pregnancy in respectively, which illustrates the significant public health problem of cigarette smoking during pregnancy in Merseyside.⁽¹⁴⁰⁾ The study examined the influence of maternal and foetal factors upon the prevalence of asthma, and found that maternal cigarette smoking predisposes children to premature birth, and that premature birth is also an independent risk factor for asthma.⁽²⁴⁾ Researchers found that these mothers were more likely to be from a lower socioeconomic background, and that mothers who smoked during pregnancy were also more likely to consume alcohol prenatally.⁽³⁸⁾ An analysis of population attributable risk for adverse birth outcomes as a result of maternal cigarette smoking during pregnancy in Merseyside demonstrated that around 25% of low birth weight deliveries and up to a sixth of premature births could be attributed to this particular risk factor.⁽¹³⁸⁾ Children exposed to cigarette smoke in utero were more likely to have a lower gestational birth weight. They also may be predisposed to short stature, behavioural problems and obesity in later childhood.^(140, 141)

Data from routine sources further supports evidence from the MRHS.^(9, 132) Children from Merseyside are exposed to a number of both modifiable and fixed risk factors for

respiratory disease, which in turn contributes to the significant respiratory morbidity in the paediatric population in Merseyside. However, the data from the MRHS only represents children aged 5-11 years, meaning data is only applicable to children of this age. Despite data being collected about pregnancy and preschool years retrospectively, this may be subject to recall bias. Furthermore, the cross-sectional study design of the MRHS means that at the point of data collection, many children had already been diagnosed with asthma, thus the precise aetiology may have been unclear. Although general population trends may be demonstrated from the series of surveys, the gross changes in respiratory symptoms on an individual level cannot be determined, and neither can causality.

The advantages of the Liverpool Respiratory Birth Cohort Study over previous studies of children in Merseyside include the longitudinal linkage of data, which will permit researchers to gain insight in to both the prevalence and possible aetiology of respiratory symptoms, but also how patterns of such symptoms change over time on an individual basis, within the Liverpool population. The questionnaire in the LRBCS also includes a section that explores quality of life in addition to the respiratory symptom questions, which allows researchers to gain insight in to the impact of respiratory conditions upon both children and their families. The study design as a birth cohort study allows exposure and demographic data to be gathered early in life, and will permit researchers to explore the previously undescribed prevalence of respiratory symptoms in Liverpool's preschool population. Table 1. 2 summarises previous longitudinal studies of respiratory diseases in paediatric populations.

Table 1. 2 Longitudinal Studies of Respiratory Diseases in Paediatric Populations

Study	Acronym	Country/Region	Year	Age	Number of Participants	Areas of Interest
Isle of White Cohort Study ⁽¹⁴²⁾	-	Isle of White, United Kingdom	1989	0+	1,456	Environmental factors, food allergies
Multi-Centre Allergy Study ⁽¹⁴³⁾	MAS	Berlin, Dusseldorf, Mainz, Freiburg and Munich, Germany	1990	0+	1,314	Asthma, Atopy and factors affecting sensitization
Leicester Respiratory Cohorts ⁽⁶⁾	-	Leicester, United Kingdom	1990 & 1998	1+	1650 & 8750	Natural history and prevalence of respiratory disease in children
Environment and Childhood Asthma ⁽¹⁴⁴⁾	ECA	Oslo, Norway	1992	0-2	3,754	Association of air pollution and asthma in young children
Manchester Asthma and Allergy Study ⁽¹²⁾	MAAS	Manchester, United Kingdom	1995	0+	957	Natural history of asthma and allergies
Prevention and incidence of asthma and mite allergy – Natural history study ⁽¹⁴⁵⁾	PIAMA	The Netherlands	1996	0+	3,291	Asthma, Respiratory symptoms, Allergies
Pollution and Asthma Risk: an Infant Study ⁽¹⁴⁶⁾	PARIS	Paris, France	2003	0+	3,855	Environmental effects upon aetiology of asthma
International Study of Asthma and Allergies in Childhood ⁽¹¹⁹⁾	ISAAC	International	1991	6/7 & 13/14	>2,000,000	Aetiology and impact of asthma and other allergic disease in childhood
Western Gothia Children Study ⁽¹⁴⁷⁾	VGB	Göteborg, Sweden	2003		4,921	Natural history and risk factors for asthma and allergies

1.5 Respiratory Symptom Questionnaires

During the formation of the protocol of the LRBCS, it was decided that the Liverpool Respiratory Symptom Questionnaire (LRSQ) would be used as the core questionnaire. It has already been validated for paediatric populations, and a unique feature of the LRSQ as a research tool is that it explores the child and family's quality of life in the context of respiratory symptoms.⁽¹⁾ The questionnaire is a fundamental element of the study design of the LRBCS, thus it was necessary to consider the context of other validated respiratory questionnaires to ensure that the LRSQ is the most appropriate tool for the LRBCS.

1.5.1 General Respiratory Symptom Questionnaires

The widespread use of respiratory symptom questionnaires to assess the prevalence of cough, wheeze, dyspnoea and other symptoms began in 1960, when the Medical Research Council (MRC) designed a questionnaire to be used in respiratory epidemiology.⁽¹⁴⁸⁾ The original questionnaire has been applied in modified forms in a number of epidemiological studies worldwide. There are now a number of respiratory symptom questionnaires that have been validated for use in adult and paediatric populations. There is wide variation in the purpose and use of questionnaires: some are disease specific whereas others explore the nature and impact of respiratory symptom. Some questionnaires are used for clinical assessment of disease progression in individuals, whereas others may be used for epidemiological surveillance in disease free populations. Questionnaires may be completed as part of a structured interview, or they may be self-completed. There are a number of widely used adult respiratory symptom questionnaires which explore the impact of respiratory symptoms upon quality of life. However, these questionnaires have not previously been validated in children, and contain domains that are unsuitable for paediatric studies, and are therefore unsuitable for the LRBCS (see Table 1.3).

1.5.2 Paediatric Respiratory Symptom Questionnaires

There are few respiratory symptoms questionnaires that assess respiratory symptoms in children.⁽¹⁴⁹⁾ Furthermore, questionnaires that are used in a paediatric context often focus upon a specific disease processes, namely asthma. as opposed to symptoms alone (see Table 1.3).

The questionnaire used in the previously discussed ISAAC study is the most frequently used respiratory symptom questionnaire for children.⁽¹²⁰⁾ This may be attributed to the large number of participants that were involved with ISAAC, and also because it has been successfully translated in to a number of languages. The questionnaire includes 21 items, and covers a number of domains, that assess the prevalence and severity of asthma,

rhinitis and eczema in childhood.⁽¹¹⁹⁾ Despite providing a comprehensive assessment of the prevalence of respiratory and allergic symptoms in children, a limitation of the ISAAC questionnaires is that there is no exploration of the impact of symptoms upon quality of life.

The American Thoracic Society (ATS) also created a paediatric respiratory questionnaire which is a widely accepted tool for assessing respiratory health in children.⁽¹⁵⁰⁾ The ATS questionnaire consists of up to 45 items that explore demographics and exposures including co-morbidities as well as personal medical history. Other questionnaires that specifically explore the prevalence, control and impact of childhood asthma include the Asthma Control Questionnaire and the Test for Respiratory and Asthma control in Kids.^(151, 152) However, these questionnaires are not appropriate for use in the LRBCS as they are designed for specific disease processes.

Like the LRSQ, The Paediatric Asthma and Quality of Life questionnaire explores both the prevalence and impact of respiratory disease in children, however it is designed and validated for the assessment of children aged 7-17 years, thus may not be suitable for the preschool population of the LRBCS.⁽¹⁵³⁾

[The Liverpool Respiratory Symptom Questionnaire](#)

The research team concluded that the LRSQ would be the most appropriate questionnaire to explore the respiratory symptoms of preschool children in the LRBCS (see Appendix 3 for original version of LRSQ). The questionnaire was developed using pre-existing standard questionnaires, including the ISAAC questionnaire, and aimed to identify up to four clinical phenotypes of wheeze in preschool children. It was first validated by Powell et al in 2002, who used the questionnaire in a group of children admitted to a specialist neonatal unit in comparison to a group of healthy controls born at the same hospital.⁽¹⁾ The initial study demonstrated that the questionnaire had good sensitivity (a range of 88.9-96.7% across all eight domains), in terms of detection of respiratory symptoms, and also had good internal consistency, with Cronbach's Alpha scores of 0.87-0.95, and short-term reliability was acceptable, with Kappa demonstrating agreement with scores ranging from 0.4-0.7. The questionnaire was further validated by Trinick et al in 2012 to assess symptoms and quality of life in 20 preschool children with cystic fibrosis, in comparison to 51 healthy preschool controls.⁽⁷⁾ Trinick also assessed the questionnaire in an older group of children aged 6-12 years, and demonstrated that children with known chronic respiratory disease (cystic fibrosis) had significantly higher LRSQ scores, particularly in the quality of life domains of the questionnaire. Children who suffered with chronic respiratory disease that frequently

missed school also had higher LRSQ scores. The internal consistency scores were slightly lower in the second study, with a range of 0.64-0.89 in the preschool group, however this was attributed to a single question relating to snoring in the night time symptoms domain (see Table 1 for overview of LRSQ domains and appendix 3 for the complete LRSQ). Powell et al also noted that this particular question demonstrated little correlation with other questions, thus the LRBCS will consider the removal of this question during analysis of the responses from our cohort. In consideration of response rates, the content and language of the LRSQ, which should take 5-10 minutes to complete, is highly acceptable to parents and caregivers. A Flesch-Kincaid reading score analysis also demonstrated that the questionnaire was an appropriate level for parental completion.

The questionnaire was further validated in an unpublished cross-sectional that explored respiratory symptoms in infants that had previously been treated for RSV bronchiolitis, which was conducted by Pickles and Semple in 2011. This study also demonstrated that the LRSQ had good internal validity and the study achieved an acceptable response rate, which suggest acceptability. The study also highlighted issues with the design and layout of the questionnaire, which can be altered in the LRBCS and were thought to have affected the quality of some of the data that was collected.

The LRSQ will be used alongside an exposures and demographics questionnaire to provide researchers with a comprehensive overview of the prevalence, nature, impact of respiratory symptoms and diseases in preschool children living in Liverpool. It may also aid researchers to identify the exposures that predispose these children to respiratory morbidity. The exposures and demographics questionnaire was created with input from academic supervisors and several senior respiratory physicians, including those who initially developed and validated the LRSQ (see appendix 4 for demographics and exposures explored in the questionnaire). Questions evaluate important risk factors for respiratory disease in infancy and childhood, including family history of atopy, exposure to cigarette smoke and postcode, which will be used to calculate the indices of multiple deprivation scores for participants.

Table 1.3 Respiratory Symptom Questionnaires

Name of Questionnaire	Abbreviation	Completion	Conditions/Symptoms Explored
Medical Research Council Respiratory Questionnaire ⁽¹⁵⁴⁾	MRCq	Self-completed or Interview	Respiratory symptoms, past medical history, smoking history, family history and occupational history.
St George's Respiratory Questionnaire ⁽⁴⁾	SGRQ	Self-completed	Chronic airways diseases, including chronic obstructive pulmonary disease,
American Thoracic Society Division of Lung Disease questionnaire ⁽¹⁵⁰⁾	ATS-DLD-78	Self-completed	Prevalence of respiratory symptoms and disease.
Asthma Control Test ⁽¹⁵⁵⁾	ACT	Self-Completed	Asthma control
International Union against Tuberculosis and Lung Disease Bronchial Symptoms Questionnaire ⁽¹⁵⁶⁾	IUATLD	Self-completed	Respiratory symptoms, bronchial symptoms, respiratory infections.
Wisconsin Upper Respiratory Symptom Survey ⁽¹⁵⁷⁾	WURSS	Self-Completed	Assess the severity of the common cold (coryzal symptoms).
Leicester Cough Questionnaire ⁽¹⁵⁸⁾	LCQ	Self-Completed	Impact of chronic cough upon quality of life
Self-Reported Chronic Respiratory Questionnaire ⁽¹⁵⁹⁾	CRQ-SR	Self-Completed	To assess the severity and impact of chronic obstructive pulmonary disease
Interviewer Led Chronic Respiratory Questionnaire ⁽¹⁵⁹⁾	CRQ-IL	Interview	To assess the severity and impact of chronic obstructive pulmonary disease

Table 1.4 Paediatric Respiratory Questionnaires

Name of Questionnaire	Abbreviation	Symptoms/Conditions Covered	Age (Years)	Completion
Liverpool Respiratory Symptom Questionnaire ⁽¹⁾	LRSQ	Chronic conditions, cough, Wheeze, shortness of breath, snoring	<5	Parental
International Study of Asthma and Allergies in Childhood questionnaire ⁽¹²¹⁾	ISAACq	Asthma and Allergic disease	6/7	Parental
International Study of Asthma and Allergies in Childhood questionnaire	ISAACq	Asthma and Allergic disease	13/14	Child
American Thoracic Society Children's Questionnaire ⁽¹⁵⁰⁾	ATS-DLD-78c	Asthma, Respiratory infections	<13	Parental
Asthma control questionnaire ⁽¹⁵¹⁾	ACQ	Asthma	6-16	Parental
Test for Respiratory and Asthma control in Kids ⁽¹⁵²⁾	TRACK	Asthma, respiratory disease	<5	Parental
Paediatric Asthma Quality of Life Questionnaire ⁽¹⁵³⁾	PAQLQ	Asthma	7-17	Parental
Pollution Effects on Asthmatic Children in Europe ⁽¹⁶⁰⁾	PEACEq	Respiratory symptoms in the context of environmental pollution	6-12	Parental
Wythenshawe Community Asthma Project Questionnaire ⁽¹⁶¹⁾	-	Asthma, undiagnosed respiratory disease	5-15	Parental
Infant/Toddler Quality of Life questionnaire ⁽²²⁾	ITQOL+ISAAC	Impact of wheezing illness in preschool children upon health related quality of life	0-5	Parental

1.6 Conclusion

Birth cohort studies are a valuable epidemiological tool to monitor the changes in prevalence of disease within populations. There have been a number of birth cohort studies conducted at regional, national and international levels across the world, which focus on the health and development of children. The results from these studies have contributed significantly to our knowledge of the determinants of health during childhood, as well as the effects in later life. They have informed governments and allowed policies to be implemented to protect and promote health in childhood. Longitudinal studies have also been conducted to specifically investigate the epidemiology of respiratory disease, asthma and allergic diseases, which have allowed a greater understanding of the risk factors and natural history of respiratory disease in children. The design of these longitudinal studies often rely upon parent-completed questionnaires to assess children at specific time points, however, existing questionnaires have limitations, and there are currently very few questionnaires that are validated for exploring respiratory symptoms in preschool children.

The LRBCS is amongst the first longitudinal studies that explores both the prevalence and impact of respiratory symptoms within an unselected population based birth cohort study, and will also be the first birth cohort study to use the LRSQ.

Chapter 2

Questionnaire Development

2.1 Introduction

During the protocol development by Pickles & Semple, it was decided that a core feature of the study design should be an online version of the LRSQ. The use of contemporary technology is hoped to improve compliance and retention of participants. Evidence suggests that using the internet (as opposed to postal methods) for epidemiological research can increase response rates, reduce loss to follow up, and improve the quality of data.^(162, 163) My involvement with the study commenced during the second of phase (Table 2.1), with the development of the questionnaire. To ensure that conducting a longitudinal study online was feasible in this population, it was first necessary to assess whether mothers from the target population of the LRBCS would consider the online format as accessible and acceptable.

Table 2.1 LRBCS Timescales

<i>Phase</i>	<i>Tasks to be completed</i>
<i>1</i>	Completion of protocol and application to IRAS for ethical approval by May 2012.
<i>2</i>	Development of the online questionnaire, email and consent forms by December 2012.
<i>3</i>	Recruitment from January 2013 for a minimum of 12 months (including 4 week pilot).
<i>4</i>	Distribution and analysis of questionnaires.

The idea to conduct the LRBCS online stemmed from the knowledge that the way the public interact with health related services and information has evolved over the last two decades. This is secondary to the advancement of the internet, paired with the ever-increasing availability of portable multimedia devices, such as laptops, tablets and smartphones.⁽¹⁶⁴⁻¹⁶⁶⁾ This provides health care professionals and researchers with the new opportunity to engage with new populations, and to gather epidemiological information outside of the paradigm of the usual experimental settings.^(167, 168) However, in comparison with other industries, the medical profession somewhat lags behind in investment and utilization of information technologies for research and development.^(169, 170) The internet provides cost-effective and simple means of conducting research and purpose-built websites can provide simple tools for creating surveys, whilst social media can be used as a platform to target wider audiences.^(171, 172)

2.1.1 Conducting Research Online

Participation in traditional methods of collecting epidemiological data, including paper questionnaires and participants interview sessions has declined in some of the established birth cohort studies over recent years.^(64, 65, 173-175) The costs of printing and distributing questionnaires may be considerable in large study populations.^(176, 177) Some of the proposed benefits of distributing research questionnaires online, in contrast to postal methods include cost-effectiveness, and some studies report improved response rates, which are desirable to any researcher conducting a birth cohort study.^(162, 163) However, there has been conflicting evidence about the validity of data collected by these methods, and thus researchers must appraise the benefits and limitations of this research method in the context of their own study and population when deciding to conduct a study all or partially online.⁽¹⁶⁷⁾

Advantages of online questionnaires in medical research studies

Conducting longitudinal research studies using the internet having significant benefits to both participants and researchers, in the context of time, costs and convenience. These benefits are beginning to be acknowledged by some of the large ongoing birth cohort studies, including ALSPAC⁽⁵⁾ and Growing up in Scotland⁽⁶⁸⁾, which have both commenced the transition to online questionnaires. Furthermore, a birth cohort study was established in Italy in 2007 that primarily used the internet to recruit participants and collect data.⁽¹⁷⁸⁾ It has so far recruited approximately 6100 mothers to the cohort, thus demonstrating that this is feasible to conduct a an epidemiological using the internet.⁽¹⁷⁹⁾

Furthermore, the quality of data may also be superior in electronic questionnaires, due to technology that prevents incomplete or implausible responses being submitted.^(167, 174) Once the logistics of online questionnaire distribution have been finalised, there is minimal need for administration. as the technology permits researchers to automate the delivery of self-administered questionnaires, and subsequent reminders if necessary, to large volumes of participants at specified time points.

Responses can be received immediately by email, HTML document or database files, which permits rapid analysis of data. This eliminates the need for interviewers or administrators, which in turn can reduce study costs. Study costs may be further reduced due to savings on printing and postage costs. The advancement of technology also permits the questions to be tailored to an individual based on responses to previous sections, which can considerably shorten the length of the questionnaire and enhance the survey experience by maximising the perceived relevance of the study to participants.

Disadvantages of online questionnaires in medical research studies

Although there are a number of advantages associated with conducting epidemiological studies online, researchers must also consider the limitations of this method of data collection.^(167, 174, 180-182) It is necessary to appraise the suitability of online data collection to their own particular study to minimise the chance of biased results. There is little data available that specifically addresses the efficacy of online questionnaires versus postal questionnaire in the context of a longitudinal prospective birth cohort study.⁽¹⁷⁸⁾ Some limitations are unavoidable and inherent in all studies that involve questionnaires, however some limitations are unique to internet based research.⁽¹⁶⁶⁾ The two major concerns with data collected online are validity and bias.⁽¹⁸⁰⁾ Selection bias is one of the most significant problems faced by researchers when conducting health-based research online.

Although self-selection bias is prevalent in traditional postal questionnaires, researchers must consider that only certain types of individuals would be likely to complete a questionnaire online, and furthermore it may not be possible for people from certain demographics to access an online questionnaire. The LRBCS attempts to overcome this bias by ensuring during feasibility testing that a large proportion of the target population have access to the internet. Furthermore, the LRBCS research team offer a postal option for communication and questionnaires for all those who have no access to the internet or prefer a paper questionnaire. Recruitment to the study will be in person, thus a number of the difficulties associated with internet based-recruitment from social media and websites are not relevant to the LRBCS.^(171, 172, 178)

Due to the aforementioned socioeconomic disparities in the city of Liverpool, a true representative sample is essential for the validity LRBCS, thus the research team will continuously monitor the demographics of participants, to monitor any underrepresentation of certain maternal age groups, parents from lower socio-economic households or minority ethnic backgrounds, which has been reported in other web-based health research.^(178, 183)

Clear benefits and limitations exist and must be considered when conducting research using online resources. The design of the LRBCS aims to identify any possible limitations of the study in its development stage, thus the study will be developed closely with parents to ensure the design appeals to potential participants.

2.1.2 Public and Patient Involvement

It is accepted that feasibility testing is an essential step of research methods, and input from members of the target population during the development phase of an

epidemiological study can be invaluable, being both practical and constructive.^(184, 185) The research team felt that it was therefore essential to develop the LRBCS involving mothers from similar demographics to potential participants. Patient and public involvement (PPI) is the name given to this process of developing health related services and projects in collaboration with patients and the wider public. This is recommended by regulatory bodies such as the Department of Health and the National Institution of Health Research (NIHR), in which, and implemented in research and development by the National Institute of Clinical Excellence (NICE).^{(186) (187, 188)} PPI is an umbrella term used to describe “the multiplicity of interactions that patients and the public have with health services”.⁽¹⁸⁹⁾ Fundamentally, it represents the effective and purposeful engagement between health care professionals, service users, and the public in all aspects of planning, developing, commissioning and decision making.⁽¹⁹⁰⁾ The process aims to enhance the quality of health care and research, and satisfaction amongst patients and participants respectively. Thus, the research team hypothesized that developing the appearance and presentation of the LRBCS with the input of potential participants will ensure that the study is developed to be both suitable and attractive to this population.

Several publications have demonstrated that the overall design is crucial in capturing the interest of participants and ensuring prompt and meaningful responses.⁽¹⁹¹⁾ The graphic “non-verbal” elements of questionnaire presentation convey important messages and instructions to participants, and therefore should also be carefully considered when designing a questionnaire.⁽¹⁹²⁾ For the LRBCS, the most appropriate design will be determined by interviewing mothers from the target population. The results from these PPI sessions with parents will guide researchers towards the final design, and it is hoped that parents consequentially will find it more desirable to continue to return the questionnaire for the whole five years, which would inevitably increase the power of the LRBCS.

2.1.3 Objectives:

To assess the accessibility and acceptability of the LRSQ and demographics questionnaire in the context of presentation, format and appearance by involving mothers.

2.2 Methods

2.2.1 Development

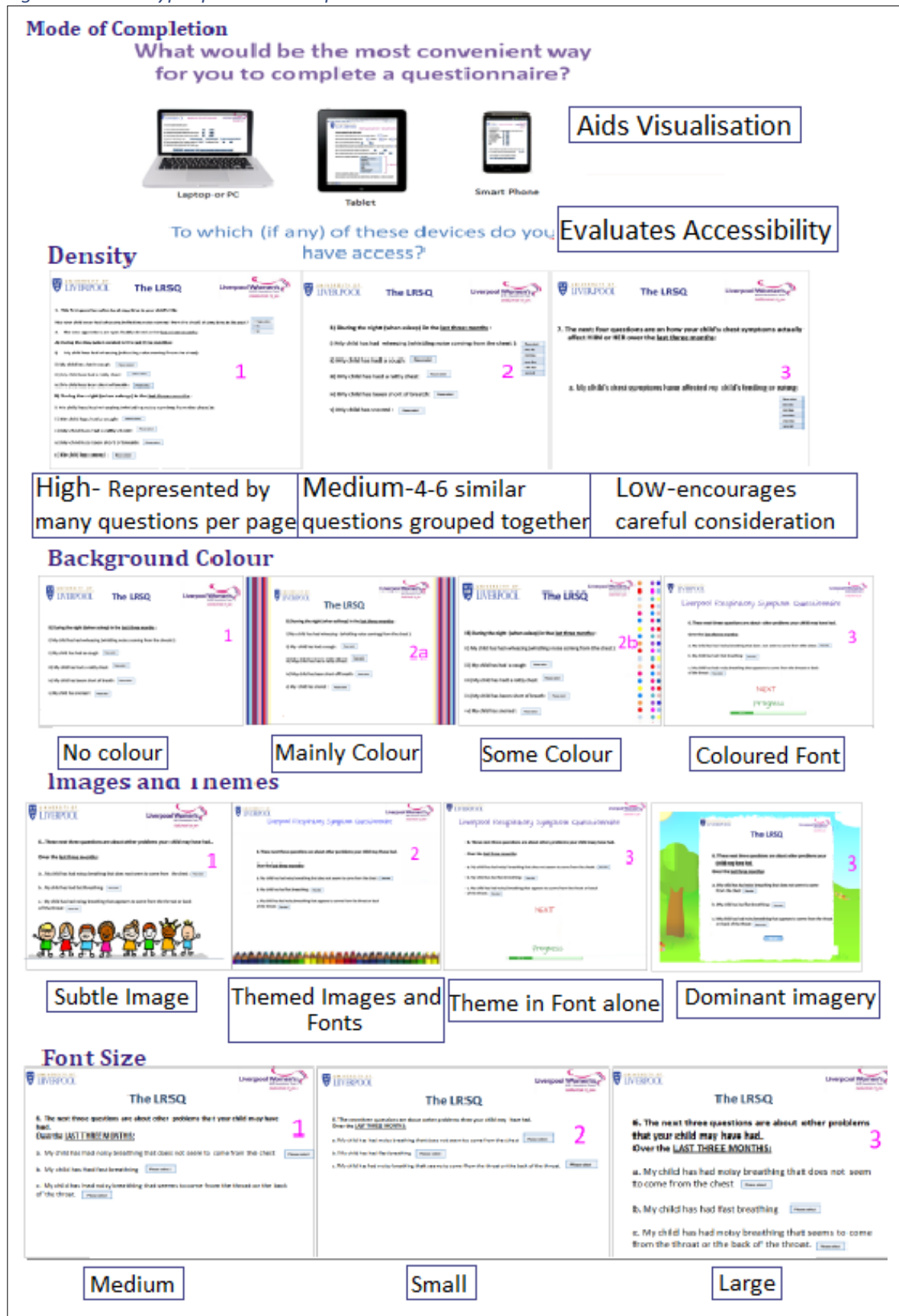
The key variables found to affect the attitude and perceptions towards a questionnaire included the layout, order and density of the questions and information presented, as well as the use of colours, patterned backgrounds, images and logos, and variation in font size and colour.⁽¹⁹¹⁻¹⁹⁴⁾ It was therefore decided that a feasibility study would be beneficial for researchers in order to appraise domains such as accessibility; whether participants could easily access and complete the questionnaire; as well as design features including density, which is the amount of information displayed on each page including the spacing between questions. Researchers would also consider the most appropriate size and style of fonts and typeface for the questionnaire. The use of images and logos or other non-verbal communication and background and colour were also to be considered. These various domains were used to create a series of questionnaire prototype pages, each with options or variations of each of these domains. Figure 2.2 demonstrates how these domains were translated in to designs.

Three to four options for each domain were created and prepared for presentation to a small group of parents in order to assess the acceptability of the format of the questionnaire, and the impact of the different designs on how the questionnaire was perceived. For maximum continuity, the parents to whom these prototypes would be presented would be from the same population as the LRBCS – English speaking parents of newborn infants at the Liverpool Women’s Hospital (LWH). Therefore, the inclusion and exclusion criteria for this small pilot were identical to that of the LRBCS (Figure 2.1). The presentation (see appendix 5) was limited to five short key questions to be answered – one for each of the previously identified domains.

Figure 2.1 Eligibility for involvement in LRBCS PPI session

- *Inclusion:* Infants born at Liverpool Women’s hospital, including premature births, where the parents normally reside in Liverpool postcodes (L1-L38) regardless of future residence
- *Exclusions:* Neonates born to parents normally resident outside the Liverpool postcodes L1-L38. Babies born to non-English speaking parents.

Figure 2.2 Prototype questionnaire presentation used in PPI session



2.3 Results

Twenty mothers that met the inclusion and exclusion criteria of the study were approached: all twenty readily volunteered to evaluate the questionnaire prototypes. Participants' preferred design for each domain were documented. It was also recorded if participants had no preference. The researchers also noted any additional comments offered by participants as this feedback is also useful.

2.3.1 Accessibility

From the outset, the intentions of the researchers involved in the LRBCS was that the study should be conducted online. As previously discussed, the availability of the internet is vastly expanding, however prior to conducting a study online, the feasibility must be explored, and researchers must ensure that participants can easily access the internet.

Of the 20 parents interviewed, most (n=13) communicated that their preferred method of completion of a questionnaire of this type would be using a laptop or personal computer (Figure 2.3). A preference to a tablet or smartphone was expressed by seven of the interviewees (n=2 and n=5, respectively). No mothers that were interviewed expressed a preference to receiving a paper questionnaire by post. All 20 interviewees confirmed that they had access to their preferred mode of completion, and 19 of the 20 had access to a personal computer. Many of the additional comments received about accessibility were involving smartphones. Many felt that despite having access to both a computer and a smartphone, they considered completion via a smartphone to be too complex. Conversely, participants that conveyed preferences to smartphones generally chose this option as they perceived it to be less time consuming as it would be available "any place, any time".

Figure 2.3 Preferred method of completion of questionnaire

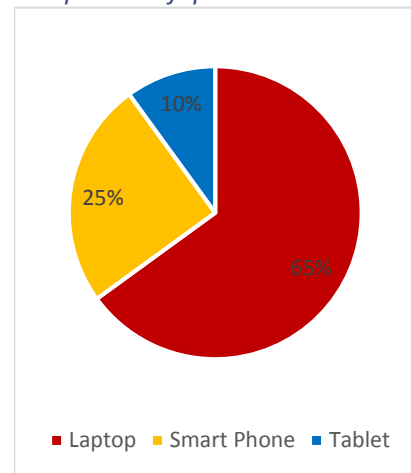
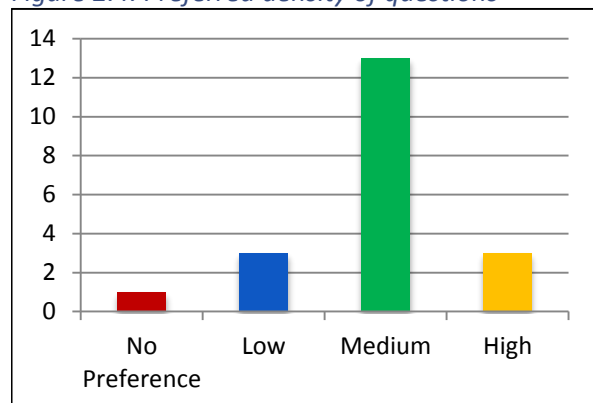


Figure 2.4. Preferred density of questions



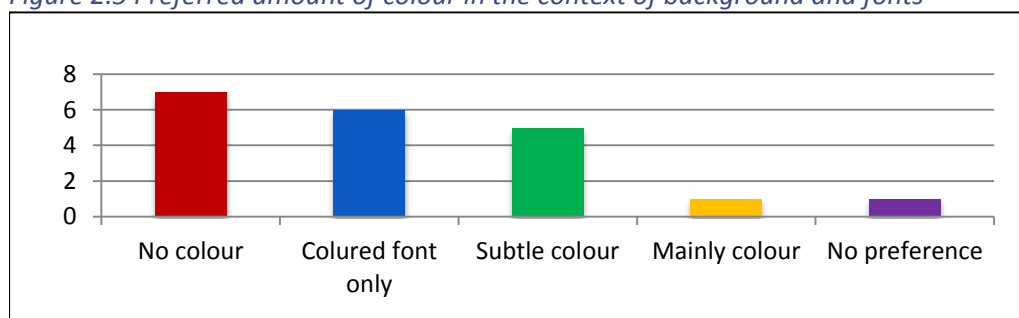
2.3.2 Density

Page density was categorized in to three alternative options: high- with many or all the questions were on one page; medium- where a few similar questions were grouped together; or low- represented by one question per page. As anticipated, a medium density was preferred by most of the participants (n=13)(Figure 2.4). This density was perceived as being efficient without being overwhelming. Three preferred a higher density and a further three participants preferred a low density. One mother expressed no preference in regards to the density of the questions. Many parents expressed their frustration in completing online questionnaires with low densities; they are perceived as “endless”; one parent stated she would be likely to stop answering the questions should a questionnaire be in this format. In contrast, some parents believe that a high density would discourage them from completing the questionnaire.

2.3.2 Background

Four sample slides with varying proportions of colour were provided for the volunteers to scrutinise, ranging from a plain white background, and a similar one with coloured fonts, to a background containing several bright colours. Seven stated a preference to a plain, uncoloured background, and six reported that they would favour a plain background with subtle colour in the fonts, whilst five wanted some colour (Figure 2.5). One wanted a very colourful background, and one stated no preference. It may be of significance that many participants hesitated prior to responding to this question, and several participants found it difficult to make a definite decision.

Figure 2.5 Preferred amount of colour in the context of background and fonts



2.3.3 Themes, Images and Logos

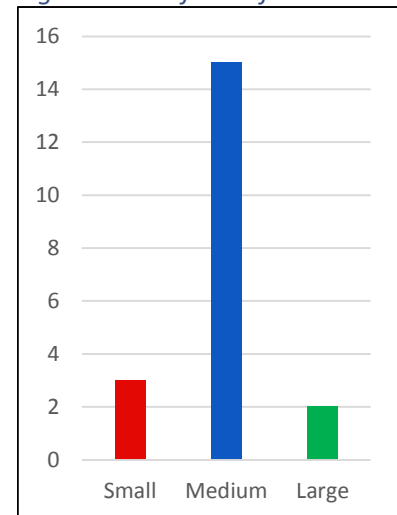
This aim of this section of the interview was to evaluate the responses evoked by the use of different images and logos. As recommended by the literature⁽¹⁹⁵⁾, the prototypes used images that were relevant to the nature of the LRBCS, and “friendly” and appropriate themes were created. The first had an image of children holding hands along the footer; the second had pencils along the footer and a header in a typeface of child-like writing. The third was very colourful and had a child-style illustration in the background. Positive responses were received by thirteen of the participants to the first theme, compared to just 2 and 1 to the second and third options respectively. Five people stated no preference to any of the above themes, and four of these communicated that they would prefer use of images to be kept minimal.

2.3.4 Font Size

The final area of questionnaire design tested was font size. Examples of the appearance of small, medium and large fonts were provided. Arial, a sans serif font was selected for testing as these fonts are perceived better when reading screens (as opposed to Serif fonts such as Times New Roman, which are better perceived on paper). Arial in specific was selected due to its wide availability in software packages. Three quarters (n=15) of the parents interviewed preferred the medium font, which corresponded to a size 16 Arial font (Figure 2.6).

Three preferred a smaller font (Arial size 12), and two preferred a larger size (Arial size 20). However, in consideration of the additional feedback and comments received, the key seems to be relativity; many of the parents expressed that it is the ratio of the typeface relative to the screen size that is important, as opposed to the actual size.

Figure 2.6 Preferred font size



2.3.5 Other Significant Findings

Many of the new mothers interviewed by LRBCS researchers demonstrated a keen interest in aiding the development of the LRBCS questionnaire, and were eager to provide feedback and suggestions for improvement or modification of the current design (Figure 2.7). Furthermore, it was encouraging to hear that many of the parents were intrigued by the study itself, and were disappointed to discover that they were not currently able to participate.

Figure 2.7 Additional Comments received from parents

- Ensure there is enough information available about the reason for the study.
- Images can be a help and hindrance: simple and relevant pictures can maintain attention, whereas too much can be distracting.
- Keep things simple, but the overall look is very important – it needs to look professional and important.
- Keep it “short and sweet”.
- Use as little as possible open “white space” questions, and try to keep to as little options as possible.
- Give an estimate at the beginning how much time it will take to complete.
- Small incentives would make parents more likely to complete the questionnaire.

2.4 Discussion

There was a positive response from both midwives and parents to the study concept, and information gathered from the PPI session will have a significant influence upon the further development of the questionnaire. Analysis of these results has provided researchers with the opportunity to maximise the potential of the LRBCS by incorporating elements of design that were positively received by the target population. The information permitted researchers to create a full mock-up questionnaire to be used in usability testing.

There was a clear trend in terms of accessibility; personal computers were clearly favoured over other devices, with 65% of the parents stating this as their preferred method of completing the questionnaire. Furthermore, 95% had access to a personal computer, confirming that the questionnaire would be accessible. It was striking that no participants wished to receive the questionnaire by post, which is testament to the revolution of the internet and its enormous power as a tool for data acquisition⁽¹⁹⁶⁾, and moreover supports the decision to conduct the LRBCS online. It is also noteworthy that, a significant proportion (25%) would favour completing the study via a Smartphone application. It is therefore reasonable to consider the possibility of the developing a mobile phone application version of the study to ensure equality and maximise accessibility. Advancement in Web technologies now provide open access to the tools required to easily create such applications.^(197, 198)

The trends seen in this study in the context of font size, density and background colour, where results deviate towards the middle or moderate option have been demonstrated in other studies, and may be influenced by participants answering in a way they perceive to be socially desired or expected by the interviewer.⁽¹⁹⁹⁾ Furthermore, the use of such terms in a research setting may be arbitrary. As the questionnaire content had been previously validated for use within this population and thus the questions will remain unchanged. However, information density can be modified, and it may affect the overall likelihood of completion of a questionnaire⁽¹⁹⁴⁾. Vast amounts of questions on one page may intimidate potential participants, whereas, as stated by some of our participants, very low densities (i.e. one question per page) can prolong the questionnaire and frustrate participants, thus raising the attrition rate of a study⁽¹⁹⁹⁾. We must therefore consider the presentation of information- a fine balance must be achieved. It is reasonable to conclude that a medium density would be most appropriate; 65% of the participants agreed. A logical method of executing this would be to group four to six precisely worded, similar questions together per page, and keeping this format constant throughout, which is compatible for the existing design and format of the LRSQ.

There was less consensus amongst participants in regard to which themes and logos, background styles and colour, were most aesthetically pleasing. This tends to reflect the personal preferences of individuals.⁽²⁰⁰⁾ However, overall, backgrounds with fewer colours and less imagery were preferred. When prototypes were ranked according to colour content, a correlation appeared between the proportion of colour and the amount of participants preferring this style (Figure 2.8). This strongly supports the use of a neutral background in the design for the questionnaire, with conservative use of colour. The opinions expressed by participants about the use of themes and logos also favoured a simpler designs, with over half (n=12) stating a preference for the simplest of the proposed designs, which contained just a small image on the foot of the page, and a quarter (n=4) had no preference. Thus, influenced by this evidence, the final design of the questionnaire will have minimal use of patterns and colours and modest, simple and clean images.

Typeface and font size will also follow a simple theme, a decision that is also heavily influenced by the input of those parents questioned. With consideration of the feedback received from parents, size will be relative to the page and the number of questions on that particular page, and efforts will be made to ensure the questionnaire looks appealing with a large enough font so that text can be easily comprehended.

Many of these findings are consistent with the findings of similar investigations, and will be considered when finalising the design. Elements of the different prototypes will be collaborated to create the best possible design, with the aim of being attractive and practical for parents whilst maintaining its scientific significance as a research tool. An example of how the input from the PPI session will be utilised in the design of the questionnaire is demonstrated in Figure 2.9.

Figure 2.8 Parent preferences of colour use in the questionnaire design

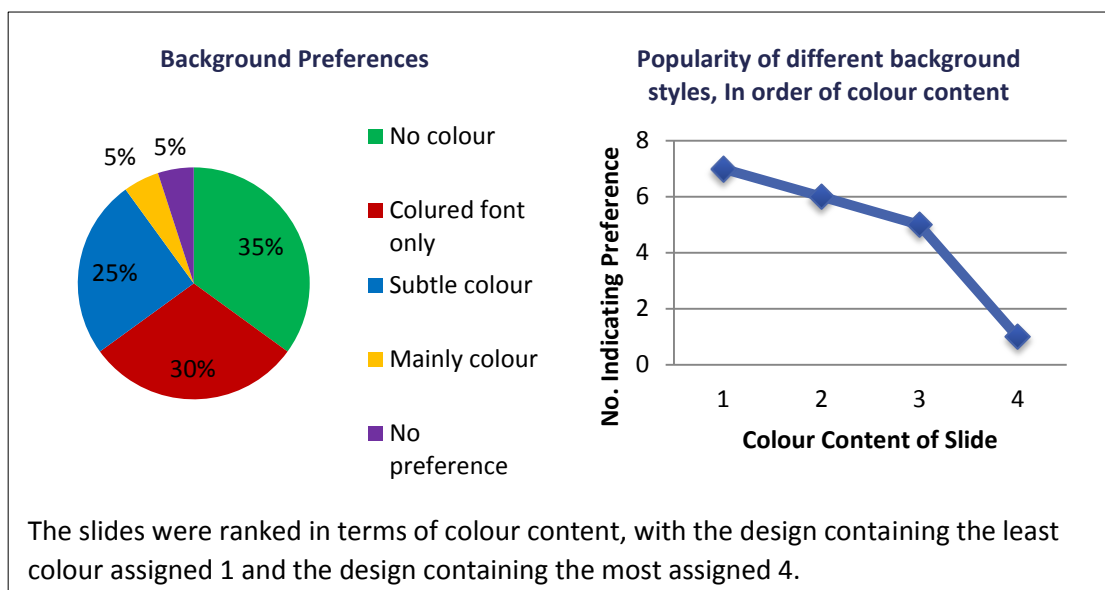
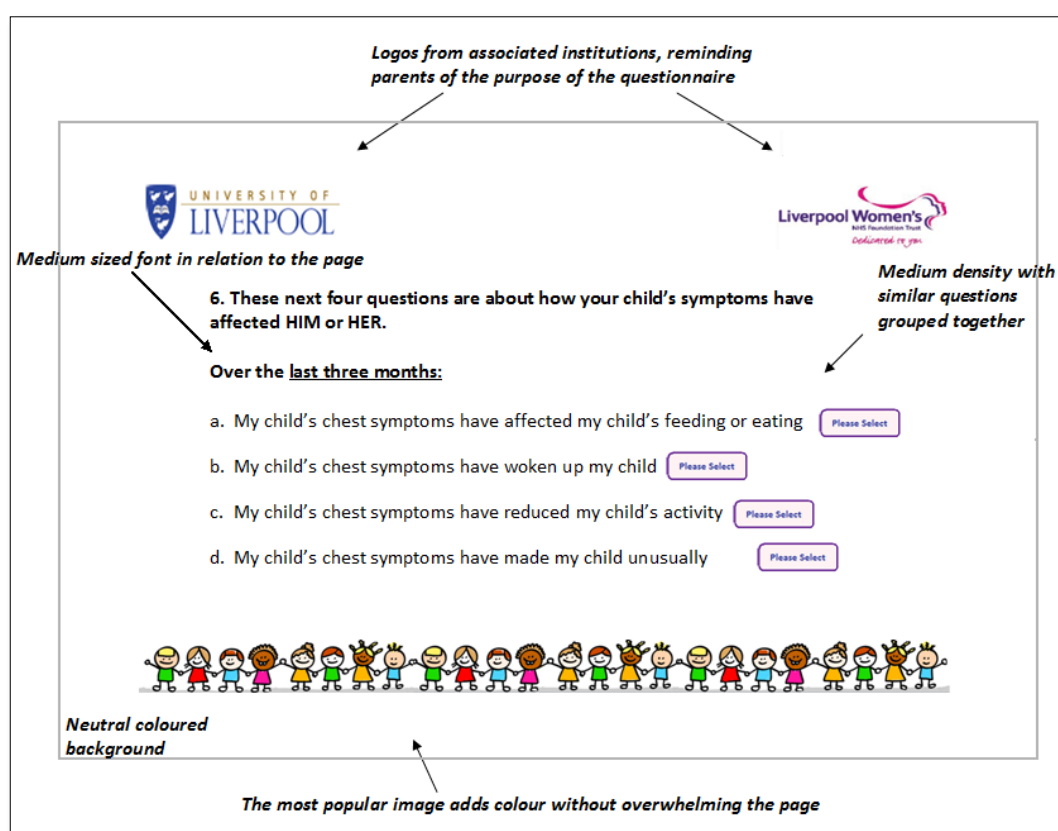


Figure 2.9 Proposed appearance of LRBCS questionnaire using data from PPI Sessions



2.5 Conclusions

2.5.1 Public and patient involvement in the development online research questionnaire:

The evidence gathered by PPI in this feasibility study supports the evidence that involving the public during the piloting and developing stages of research questionnaires can be informative and constructive. This notion permits researchers to adapt the study design to ensure participants perceive the study to be both relevant and significant. Receiving feedback will also allow researchers to tailor the LRBCS to the demands of its study population – it is hoped that this will maximise its potential in terms of response rate, attrition and the overall quality of the information gathered. This research method is perceived as new and exciting by participants and clinicians alike; it allows parents to feel empowered by their contribution in to health services, and thus increases their likelihood to partake in research.

2.5.2 Limitations of this feasibility study

Consideration of limitations is essential when appraising the quality of the data from any study. An important factor to consider is that the information was gathered by persons involved in LRBCS, which may have introduced an element of observer bias in the collection and interpretation of the information provided by parents. The risk of introducing this type of bias was lessened by the presence of two interviewers that recorded the evidence separately, however the risk may have been further minimised by recording the conversations held with parents.

When parents were interviewed, they were asked to state one preference for each of the domains; however a preferential system, whereby participants rank all the options in order of preference, may have yielded more accurate results by revealing overall trends and providing more data for robust statistical analysis.

This study targeted a specific population group, thus inferences made may not represent the whole population. Furthermore, results may have been more reliable with a larger sample size, which was not possible at the time due to time constraints. The study will be further piloted to assess usability prior to its launch, which may reveal any issues not identified in this feasibility study.

Chapter 3

Further Development of Online Materials and Preparation for Recruitment

3.1 Introduction

Until recently, creating and conducting research questionnaires using the online platform of the World Wide Web (WWW) was considered a time-consuming task requiring a considerable understanding of internet authoring programs or Hypertext Markup Language (HTML), which is the standardized system used to achieve font, colours, graphics and links on internet pages.⁽¹⁸²⁾ Today, survey software packages or online services have become easily accessible at a reasonable cost, permitting online research projects to feasibly be conducted by researchers from a variety of disciplines and backgrounds with little or no prior experience of web design.⁽²⁰¹⁾

Following the patient and public involvement work, it was necessary to develop a functional questionnaire using an online platform that was suitable for the needs of the LRBCS. The research team had prior permission to use a software package called SelectSurvey.NET (SSN) through an institutional license held by the University of Liverpool. However, despite being an acceptable platform for conducting surveys, the software had limitations, particularly in the context of freedom to design the appearance of the questionnaire, but also in the terms of the sophistication of technology. It was therefore necessary to assess whether this software was suitable for the LRBCS, as a key aim of the study was to utilize the latest technology to maximise the perceived convenience of participation for parents.

3.2 Survey Software

As the LRBCS is a longitudinal study, parents will be expected to repeatedly complete questionnaires over an extended period of time. Selection of survey software is therefore a fundamental element of the study design, as less sophisticated or inappropriate survey software may be less appealing to parents which, the research team hypothesize, could affect response rates of follow-up questionnaires and the overall impression and impact of the study. It is expected that all software should have basic question styles in order to collect the correct data, such as matrixes, drop-down menus, single or multiple choice buttons (see Appendix 6 for examples of these question types). However, with the evolution of survey software technology, a number of advanced features have emerged that enhance survey experience for participants.

3.2.1 Available Features

Many software companies offer a number of features that can be utilized to enhance online questionnaires. Some of these features are standard in all software, whereas others may only be available in premium products. These features are designed to enhance response rates or the general experience by presenting an aesthetically pleasing survey or to add company branding, or they may shorten the length of the questionnaire by omitting irrelevant sections automatically.

Flexible Design and Appearance Previous research and feasibility studies from the LRBCS demonstrated the significance of an attractive questionnaire, and that images and logos may affect how a participant perceives the study. It is thus desirable that survey software permits researchers to edit colours, fonts and headings, and additionally insert logos or relevant images.

Conditional Branching This feature permits researchers to alter the course that respondents take through a survey, based on their previous responses. This can be achieved by inserting “Skip Logic” to pages of a questionnaire, which allows irrelevant sections to be automatically omitted. This enhances the survey experience for participants, as it can significantly reduce the time taken to complete the questionnaire, and it may prevent participants from becoming frustrated or confused by the questionnaire.

Question and Answer Piping This maximises the control that researchers have over the precise wording of questions by automatically integrating a response from a previous question in a subsequent follow-up question. This feature can also be used to personalise questionnaires by “piping” a participants name in to questions.

Field Validation This is the incorporation of tools that automatically validate responses prior to questionnaire submission, which can aid researcher during the analysis of results. Examples of field validation include having an “@” in an email address, or ensuring responses are in a numerical or typed letter formats. Some software also is able to highlight if a question response contradicts a previous answer, or is implausible in any other way.

Compulsory Fields An extension of field validation is the compulsory field. This forces completion of a data field as participants are not able to submit incomplete questionnaires.

Data Analysis Survey software aids researchers in the analysis of responses to varying degrees, however as a minimum survey software should collate responses in to a comprehensive database that can be exported for analysis. Some software will offer simple

reports that summarise responses to each question, and others may offer complex statistical analysis.

Security Depending on the purpose of a questionnaire, sensitive demographic or personal data may be collected by researchers. Therefore, to uphold confidentiality and protect data it is necessary for online survey software to be secured. A minimum expectation is that the survey is secured by Secure Sockets Layer (SSL) encryption and server authentication, which ensure that data can only be accessed by authorized people, which in this context is the research team. It is also presumed that the servers that host the survey are secured using firewalls and other advanced technologies, and that they are also physically protected.

3.2.2 Survey Software Testing

Internet searches using established search engines using keywords such as “survey software” or “online questionnaire” reveals several hundred websites that offer survey questionnaire services. It was therefore necessary to appraise the suitability of these services for hosting the LRBCS questionnaires the features and services offered by these survey software websites, as well as sites that offered online form tools, as these have similar functions to survey sites, but may offer more flexibility.

Features of SSN software were the used as the baseline for comparison of various software characteristics, as this software was available without cost to the research team with specialised support from the information technology (IT) department at the University of Liverpool. A large proportion of alternative survey software including Survey Methods, Smart-Survey™, Qualtrics®, KwikSurveys, SurveyGizmo®, Microsoft® Access, Wufoo®, Formsite®, WordPress.Org Visual Form Builder, EmailMeForm™, amongst others were excluded as they offered no advantages over SSN in terms of sophistication of the technology. The features of the remaining software were briefly appraised by a member of the research team and a shortlist of four potential services was created; SelectSurvey.NET, Google Docs, SurveyMonkey® and Adobe® FormsCentral. Researchers then explored these services in greater detail, and attempted to create live versions of the questionnaires using each to establish the feasibility of using the programmes in the study. See table 3.1 for the summary of results.

Table 3.1 Comparison of Survey Software features

	SelectSurvey.NET	Google Docs	Adobe® FormsCentral	SurveyMonkey®
Price (annually)	University funded	Free	£105.39	£299
Usability	Fair	Good	Excellent	Good
Appearance formatting	Colour	Templates	Unlimited	Templates
Skip Logic - question	No	No	Yes	Yes
Skip Logic – page	Yes	No	Yes	Yes
Question Piping	Yes	No	No	Yes
Answer Pre-Population	No	No	No	Some
Help text	No	Yes	Yes	No
Logos and images	1 (top of page)	No	Unlimited	1 (top of page)
Field Validation	Yes	No	Yes	Yes
Integrated email	Limited	No	No	Limited
Security	Encrypted	Data cloud	SSL encryption	SSL Encryption
Statistical analysis	SPSS export	Excel export	SPSS export	SPSS export
Data Export	Yes	Yes	Yes	Yes
Data Summary	Yes	Yes	Yes	Yes
Progress Bar	Yes	No	Yes	Yes
Telephone/Email Support	Via University	No	Both	Email

Researchers then contrasted the strengths and limitations of each product. The software provided by the researchers' institution, SelectSurvey.NET, by Class Apps

(<http://selectsurvey.net/>), was secure and facilitated the creation of basic surveys.

However, extensive telephone support was required to incorporate advanced features such as insertion of a logo and changing the colour schemes. Despite a number of guided attempts, researchers were not able to use the piping feature. This feature was highly desirable; it permits for an answer to a preceding question can be incorporated in to a subsequent question. This feature would allow the name of the child could be used to minimise confusion with any other child a mother may have, therefore it was disappointing that the research team could not use this function. A variety of question types were possible, including check boxes and multiple selection questions, however drop-down boxes, which were the types of questions the research team had originally intended for the online questionnaire, could not easily be incorporated in to the questionnaire. Researchers successfully created a prototype questionnaire that functioned well.

Google Docs (<http://docs.google.com>) is a free, web-based service with word-processing, spreadsheet, presentation and form building and data storage functions offered by Google. Researchers were able to successfully create a complete online version of the questionnaire used in the LRBCS in less than an hour. The service offered a number of

templates and colour schemes for the form, however it did not permit the incorporation of logos or other customizable features. The questionnaire had a clean, modern feel, and was easy to complete. Furthermore, at least two studies have reported success using Google Docs as a research tool to conduct medical research.^(197, 198) However, the research team ultimately decided to exclude Google Docs as a possible research tool due to a number of concerns regarding the security of the service, and furthermore, a number of the features available on SSN were not possible on Google Docs.⁽²⁰²⁾

The LRBCS research team were also able to create a questionnaire using Adobe® FormsCentral (AFC) (<http://www.acrobat.com/formscentral>). This product is a relatively new service offered by the software company Adobe®. The software has the benefits of having a modern interface and it uses a drag-and-drop editor, whereby a user can easily “grab” an item using the computer mouse and move section, as well as easily adding or replicating items, which makes the software highly usable and easy to understand. In addition to being extremely easy to edit, AFC permitted an unlimited amount of images, logos and text, as well as all anticipated question types including checkboxes, radio buttons and drop-down boxes, except matrix questions. Similarly to Google Docs, the research team were able to create a functioning questionnaire very rapidly, and it is of significance that this was the only software that the researchers were able to successfully create a questionnaire that resembled the optimal design identified in the PPI session at Liverpool Women’s Hospital. Like the other software, AFC collated results in to an exportable spreadsheet, but in addition to this it creates a summary report for rapid summary analysis.

The final software that the research team used was SurveyMonkey® (<http://www.surveymonkey.com/>), which is arguably the most well-known of all online survey software. The software has the ability to collect data from a large number of participants, and allowed researchers some freedom in the context of questionnaire design, including font size, colour and the insertion of a logo or header at the top of the questionnaire at the time of testing (new features to incorporate some images have since been added to the software). The software has all the expected functions of survey software, including a variety of question types, and additionally has more intelligent functions including skip logic on questions and pages. However, the benefits of SurveyMonkey® were reflected in its pricing. Furthermore, once a prototype questionnaire had been created using the software, its overall appearance and feel did not differ significantly from SSN. The research team also experienced difficulty in contacting and obtaining response from the support team for the software, which was considered a

potentially significant problem in a longitudinal study where the function of the questionnaire was a fundamental element of the study design. It was thus decided that any benefit of using the SurveyMonkey® software was outweighed by its limitations, and thus it was decided that this particular software would not be used for the LRBCS.

Following the success of the previous PPI work, and considering the aforementioned benefits of involving the public in the development stages of medical research studies, the research team had planned to conduct a second study using the full version of the questionnaire prior to commencing recruitment. The research team felt that both AFC and SSN had benefits and limitations in different respects. Despite informal opportunistic feedback from colleagues, including senior respiratory physicians, indicating that AFC was overall a better software package for both participants and researchers, it was still necessary to appraise whether the advantages of this software over SSN were significant enough to warrant the costs of purchasing the product. It was also necessary to consider whether mothers from the LRBCS demographic considered AFC or SSN to be more user-friendly and to be in an acceptable format.

A feasibility study was therefore designed to ultimately decide which survey software would be used in the LRBCS. In addition to appraising the appearance and functionality of AFC and SSN, the second feasibility study also aimed to confirm whether mothers were had access to the internet, were willing to complete an online questionnaire, and whether they were confident in using the technology.

3.3 Distribution of Questionnaires

During this phase of development, it was also necessary to investigate the precise logistics of questionnaire deployment in the context of automated emails. It was necessary to investigate whether these would be an extension of survey software, additional software, or if it could be achieved using scheduling and mail merging on Microsoft Outlook, which the research team could access at no cost through the University of Liverpool. The term mail merge refers to the automatic addition of personalised fields, including names or other details that are held in a database, to communications such as letters or emails. This facilitates the mass distribution of personalised communications without requiring manual input.

The research team anticipated that large volumes of questionnaires would be sent on a rolling basis over an extended period of time. It was felt that automated email questionnaire invitations and reminders were essential to minimise the potential administrative burdens of the birth cohort study as questionnaires were to be administered to parents every six months, commencing from the fourth month of their child's life until

age five years. To ensure the success of the LRBCS, the research team required robust and reliable system for distributing links to the online questionnaire using electronic mail.

It was also imperative for software to have the capacity to personalise emails to include names and a unique identification code for the questionnaire. The unique identification is necessary for the purposes of longitudinal linkage of questionnaire data, but personalisation is also beneficial as adopting a personal approach in communications can enhance response rates in birth cohort studies ^(64, 65) .

None of the survey software options that the research team explored had an integrated email system that would be suitable for the LRBCS. Although some of the mailing requirements of the study could be met with a simple email merge, this would require date calculations for five years of follow up to be entered manually for each participant. The study has a maximum recruitment strategy of potentially 8,500 participants per year. A manual entry process is not practical and could result in human error leading to surveys being sent at incorrect dates. To facilitate the delivery of email, this system would also rely upon a researcher's personal computer being switched on at the specified date and time, which is also highly impractical.

An internet search for suitable software was therefore commenced by the research team to identify suitable email distribution software. The requirements of the research team for software that provided adequate service and security at an acceptable cost proved arduous, partially due to the inexperience of the research team. The research team had not anticipated these difficulties during the protocol development, thus the study design was partially based on a concept in the absence of experience of the types of software available.

Despite these difficulties, the research team identified email marketing services as potentially being suitable for online questionnaire distribution. These are used by businesses to engage customers and distribute marketing material and newsletters. These services offer advanced mailing list management, including some of the key features required by the LRBCS. Some email marketers offered advanced scheduling of emails, with fully automated triggering based on a specified event, such as a date of birth, or as a result of the recipients behaviour, such as clicking on a specific link within the email. Other email services required Application Programming Interface (API) to incorporate these desired custom feature, but this requires some background knowledge of application programming. The cost of purchasing this software or services often reflected the amount of input and experience required. It was therefore necessary to appraise the features of available software, and identify the most appropriate software for the LRBCS team by balancing

functionality and usability. There is great variation in the pricing of these services, which varies from one-off or monthly fees, or may depend upon the volume of emails sent or the number of subscribers.

Deliverability is another key feature that must be appraised when selecting mailing software that delivers large volumes of email messages. Deliverability is the mode of measuring the ability of an email marketing service to consistently successfully deliver email campaigns to the inboxes of subscribers. Issues with deliverability may arise as a result of large volumes of emails sent from one Internet Protocol (IP) address. Emails may be prevented from arriving a participants inbox due to their Internet Service Provider (ISP) or their own email application (such as Google Mail or Hotmail) misidentifying the email as unsolicited junk or “Spam” email.

The features and pricing of a number of products and services were investigated, including Qualtrics®, Campaign Monitor, AWeber Communications, Mail Zulu®, Boomerang®, MailChimp®, Adestra, Vertical Response, JangoMail, iContact, Benchmark Email, Pinpointe, Constant Contact® and Get Response. Due to the anticipated number of participants that would be subscribed to these mailing lists, and the volume of messages that would be sent to each participant on an annual basis, it became evident that a service offering pay-as-you-go (PAYG) options, whereby email credits are purchased as required, were the most prudent choice for emailing. Of the remaining options, a number of the services did not offer the full range of services, such as autoresponders, were not available on PAYG plans. Others had poor reviews in the context of security, usability, customisation or deliverability, and customers complained of emails being filtered by clients’ junk mail filters.

3.3.1 MailChimp®

After consideration of the benefits and limitations of the various emailing services available, the research team decided that MailChimp® would be the best option for distribution of questionnaire links. This service hosts email lists on a secure online server, and offers two-tiered security at no extra cost. The fully-automated service can schedule emails from the information held in its database – thus allowing for all future mailings to be set up at the initial sign up, without the need to calculate dates. A member of the research team can easily set up all future emails to be sent at specific intervals from a date held in the database, such as the child’s date of birth, thus ensuring invitations for survey completion are deployed at precisely the correct time to the correct participants.

The service will also allow the research team to track whether individual participants have opened emails, and whether the link to the survey been opened. It also

expresses the overall “open-rate” as a percentage. These features will allow the team to continuously monitor email performance statistics, and recognise poor response rates or any increases in drop-out, and will therefore allow them to address these issues promptly.

MailChimp® allows recipients to exercise autonomy by removing themselves from the email list, which indicates to the research team that a participant would like to remove themselves from the study. This addresses the right of the participant to withdraw from the study at any time, consistent with the ethical approval obtained. Reports can be sent in real-time or on a daily basis to the research team detailing which participants have removed themselves from the study, again identifying the research team to identify problems promptly. If desired, the technology will allow the research team to ask participants to specify why they want to leave the study. Conversely, the software also permits participants to self-enrol, by hosting subscription forms, which include a Quick Response (QR) code, which is a bar code that can be displayed on posters or other material, which can be scanned using a smartphone. When scanned, these codes will display an online sign-up form on the telephone screen. These online forms are directly linked to the study database, and the technology allows for notifications to be sent directly to the research team when details are submitted online. The research team considered the incorporation of this QR code could in to the recruitment materials to further aid recruitment.

MailChimp® allows the research team to create emails using the same branding as the survey, using the Liverpool Women’s Hospital and University of Liverpool logos, which will give the emails a professional branded appearance that hopefully will be recognised instantly by participants. There are unlimited merge fields, which allow the research team to personally address the email to parents, and contain the name of their child and the unique identification number. Replies to these automated emails will be sent directly to the research teams’ email inbox.

3.4 Development of Recruitment Material

Recruitment material such as information postcards and posters, are an essential component of the LRBCS recruitment strategy. A version of the patient postcard had been approved during the study’s review by a research ethics committee, however the appearance of this postcard was not consistent with that of the questionnaire. It is desirable for all materials to be cohesive with the questionnaires and emails in order to establish a recognisable and attractive theme for the LRBCS, which parents would associate with the study. During the period of development of recruitment material, it was decided that the full name of the study, The Liverpool Respiratory Birth Cohort Study, was too long


and may be confusing for lay people. It was therefore decided that the study would have a second, parent-friendly name in addition to the full name, which would be displayed on recruitment material, questionnaires and emails. It was felt that The Liverpool Baby Breathing Study accurately described the study in a parent friendly way.

The appearance of the recruitment postcard was therefore modified and developed to incorporate the theme and second name of the LRBCS. The research team also integrated the QR code in to the postcard design, which would provide mothers with an alternative option for expressing interest in the study. See Figure 3.1 for the original and redesigned versions of the patient information and recruitment postcard.


The research team also developed an A3 sized recruitment poster to be displayed in patient areas that also had a similar appearance and content to the other material. The aim of the poster was to increase awareness of the study and to raise the profile of the LRBCS amongst staff and patients at LWH. The poster also included a large version of the QR code, and step-by-step instructions how to scan the code in order to sign up to the study (Figure 3.2). The research team are not aware of any previous medical studies that have used QR codes to facilitate recruitment, thus the LRBCS may provide some evidence as to whether this is a feasible method of recruiting in this particular population.

Figure 3.1 Original and Redesigned Versions of the Patient Information and Recruitment Postcard

Original (Version 1) Recruitment Postcard Side 1



YOU ARE INVITED TO JOIN THE....



The Liverpool Respiratory Birth Cohort Study

The Liverpool Respiratory Birth Cohort Study will study the respiratory symptoms (colds, wheezing, coughing and difficulty breathing) of children born in Liverpool from birth to the age of five years.


- We will send you a questionnaire, twice a year, for five years.
- This should take no more than 10 minutes to fill out.
- Your decision to participate will not affect your future care.
- All responses and details are handled in confidence.
- You can chose to leave the study at any stage

Why are we doing this? We would like to find out more about respiratory symptoms, such as wheezing, coughing, that your child experiences and their effect on you and your family. We would also like to understand how these symptoms change over time and what makes them more or less likely to occur.


Why have I been chosen?
We are only asking all parents of children born at the Liverpool Woman's Hospital who were living within the L1-38 postcodes when their child was born.

Date 02/02/2012 – Version 1.0

Original (Version 1) Recruitment Postcard Side 2



THANK YOU FOR YOUR INTEREST



The Liverpool Respiratory Birth Cohort Study

Baby's*: First Name _____ Surname _____

Mothers*: First Name _____ Surname _____

Fathers: First Name _____ Surname _____

Email Address*: _____

Home Number*: _____

Mobile Number: _____

Postcode*: _____

By providing my details I agree for the researchers stated to contact me about this study.

The Research Team

Miss Rosanna Pickles *Mphil Student at the Institute of Translational Medicine*

Dr Calum Semple *Senior Lecturer in Child Health and Respiratory Paediatric Clinician*


Dr Kevin Southern *Senior Lecturer in Child Health and Respiratory Paediatric Clinician*

Professor Ben Shaw *Consultant in Respiratory and Neonatal Paediatrics*

Please affix hospital label here


I would prefer to be contacted by **POST** ☐ rather than by email

I am happy to be contacted ☐



Date 02/02/2012 – Version 1.0

Redesigned (Version 2) Recruitment Postcard Side 1




UNIVERSITY OF
LIVERPOOL

Thank you for your interest in the....

Liverpool Baby Breathing Study

The Liverpool Respiratory Birth Cohort Study



Liverpool Women's
NHS Foundation Trust

Dedicated to you


The Liverpool Baby Breathing Study will study the respiratory symptoms (colds, coughs, wheezing and breathing problems) of children born in Liverpool from when they are born until they are five years old.

Why are we doing this?
We want to find out more about the respiratory symptoms, such as wheezing and coughing that your child experiences and their effect on your family. The aim of our study is to try to understand how these symptoms change over time and what makes them more or less likely to occur.

Why have I been chosen?
We are asking all parents of children born at the Liverpool Women's Hospital who are living within the **L1-L38 postcodes only**, if they would like to take part. We are particularly interested in the children of Liverpool as there are high levels of respiratory diseases such as asthma and bronchiolitis.

If you agree to take part:

- We will send you a questionnaire online or by post twice a year, for five years
- The first questionnaire should take less than 10 minutes to complete
- Each follow-up questionnaire should take less than 5 minutes to complete
- Your decision to participate will not affect you or your child's future care in any way
- All responses and personal details will be handled in the strictest confidence
- You may choose to leave the study at any time



Redesigned (Version 2) Recruitment Postcard Side 2



UNIVERSITY OF
LIVERPOOL

Thank you for your interest in the....

Liverpool Baby Breathing Study

The Liverpool Respiratory Birth Cohort Study



Liverpool Women's
NHS Foundation Trust

Dedicated to you

To register your interest in the **Liverpool Baby Breathing Study** simply fill in your details below, and give this card to a member of staff, or pop it in the collection box. Alternatively, you can enter your details online by scanning the QR code.

Baby's First Name: _____	Last Name: _____
Baby's Date of Birth: _____	Singleton: <input type="checkbox"/> Twin: <input type="checkbox"/> Triplet: <input type="checkbox"/>
Mother's First Name: _____	Last Name: _____
Email: _____	Postcode: L _____
Main telephone number: _____	Please contact me by: email <input type="checkbox"/> post <input type="checkbox"/>



Please scan this code
using your QR reader

By providing these details I agree to be contacted by the Research team.

Don't worry, you are not committing yourself to join the study at this stage!

We will contact you in four months time to confirm that you are still interested!

If you would like any further information, you can contact the research team directly by emailing BabyStudy@liv.ac.uk or calling (0151) 2824532.

Affix Hospital Label Here



Figure 3.2 LRBCS Poster



You are invited to participate in...

The Liverpool Baby Breathing Study

The Liverpool Respiratory Birth Cohort Study

Have you recently had a baby here at Liverpool Women's?
Do you live in a Liverpool post code (L1-L38)?

The Liverpool Baby Breathing Study...
will study the respiratory symptoms (colds, coughs, wheezing and breathing problems) of children born in Liverpool from birth to the age of five years.

Interested?
Ask for one of the sign-up **postcards** that are available on Jeffcoate ward, Matbase or the Neonatal unit.

OR

Scan this QR code using the instructions below and sign up using our online form!

Step 1 - Go to your app store on your smartphone and search for a "QR" or "Scanner".

Step 2 - Download the highest rated free QR scanner

Step 3 - Once downloaded, OPEN the app and follow the instructions. You will need to aim your camera at the QR code and scan/photograph the QR code

Step 4 - You'll be taken to the sign up form for the study- enter your details here to take part!!



Sign-up QR code

What will it involve?
A short online or postal questionnaire, twice a year, for five years

Why are we doing this?
We want to find out more about the respiratory symptoms that your child experiences and their affect on your family, how these symptoms change over time and what makes them more or less likely to occur.

Questions?
If you would like further information, please email the research team at BabyStudy@liverpool.ac.uk or call (0151) 282 4532



3.5 Feasibility Testing

Following the initial feasibility study, the research team had successfully developed the concept of the LRBCS in to a functioning online questionnaire, a functioning mailing system and had also created draft versions of recruitment material. Despite having previously assessed whether mothers from the study's target demographic would be willing to complete an online questionnaire, it was necessary to confirm whether mothers could in reality complete the questionnaire, and whether there was any ambiguity in the wording or terms used. Furthermore, the research team aimed to identify whether the appearance of the questionnaires and other study material was in an attractive and understandable format for parents from all backgrounds, and to identify whether the LRBCS questionnaires should be hosted by Adobe FormsCentral or Select Survey.NET.

The research team developed a short set of questions for the semi-structured interview session with new mothers, with the aim of objectively assessing if the LRBCS questionnaire was acceptable to mothers, and to determine which survey software would be most appropriate for the LRBCS.

3.5.1 Aims

The research team aimed to conduct semi-structured interviews with mothers of neonates at LWH in a similar method to the initial feasibility study, in order to further assess the feasibility of the planned methods of the LRBCS and to determine which survey software should be selected for hosting the online questionnaires for the LRBCS.

3.5.2 Methods

The second feasibility study was conducted with sixteen new mothers at LWH on the 8th and 9th of October 2012. Appropriate patients were selected by senior midwives or ward managers, and were subsequently approached by research students for individual interviews. Research students briefly explained the background of the LRBCS, and would clarify that that mothers were not being approached for participation in the LRBCS. In order to minimise bias, the research team alternated the testing order of software; thus, in total eight mothers completed AFC first, followed by SSN, and eight mothers were asked to complete SSN followed by AFC. After obtaining verbal consent for feasibility study participation, and confirming that the mother would be eligible for the LRBCS, participants were asked to complete the complete online version of the initial questionnaire hosted by both AFC and SSN software using a tablet device. Participants were advised that the research team would not be able to help them to complete the questionnaire. Time permitting, the research students also aimed to use the opportunity to receive feedback about the appearance and content of the recruitment and patient information postcards

and posters. Mothers were asked the pre-determined questions (Figure 3.3) objectively without the use of emotive terms that may introduce bias. There was no limit to the amount of time available to the subject to complete the online questionnaires or respond to the researchers questions and give a response. To avoid bias in data collection, responses to questions were recorded separately by both researchers. The research team alternated whether the AFC or SSN questionnaire was completed first with each participant. At the end of the interview, the research team summarised responses with participants, and the researchers also discussed responses after vacating the patient room to ensure there were no discrepancies in the interpretation of results.

Figure 3.3 Questions used in the semi-structured interview of the second feasibility study

<p><i>Before Questionnaire completion</i></p> <hr/> <ol style="list-style-type: none"> 1. First impression of questionnaire (positive or negative) 2. Rating of appearance (Scale 1-10) 3. Readability of the text <hr/> <p><i>During Questionnaire Completion</i></p> <hr/> <ol style="list-style-type: none"> 1. Are the instructions clear 2. Understanding of information, questions and terms 3. Flow of questions – is it logical 4. Any vague or ambiguous questions 5. Is it repetitive 6. Any particular like or dislikes in terms of content or appearance <hr/> <p><i>After Questionnaire completion on first survey software</i></p> <hr/> <ol style="list-style-type: none"> 1. Was the length of the questionnaire acceptable 2. Overall rating of appearance of questionnaire (scale 1-10) <hr/> <p><i>After completion of questionnaire on both survey software</i></p> <hr/> <ol style="list-style-type: none"> 1. Overall preference 2. Question preference – Matrix tables or drop-down boxes 3. Any additional comment <hr/> <p><i>After reviewing recruitment material (time permitting)</i></p> <hr/> <ol style="list-style-type: none"> 1. General impression of recruitment material 2. Is the information clear and readable 3. QR codes: do they recognise them, know how to use them, and do they use them 4. Any other factors that would affect their likelihood to complete the questionnaire

3.5.3 Results

The research team successfully completed interviews with sixteen new mothers that met the exclusion and inclusion criteria of the LRBCS. A further four interviews were commenced but were abandoned as mothers were unwilling to complete the second questionnaire, thus the data is not usable as mothers would not be able to contrast AFC and SSN. Due to time constraints, it was only possible to demonstrate the recruitment material to 12 out of the 16 mothers. All mothers that were approached were happy and competent to complete an online version of the questionnaire.

Before completing the questionnaire

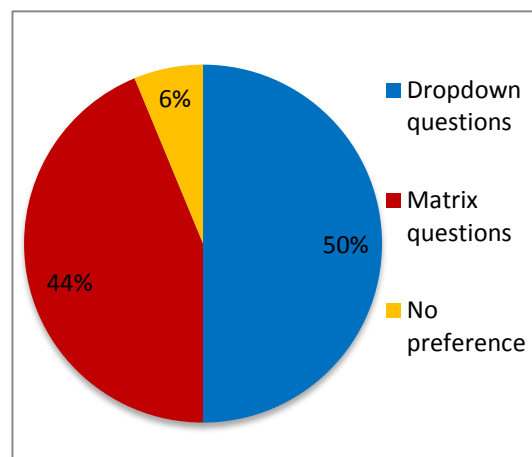
The results from the 16 mothers that successfully completed both questionnaires and the semi-structured interview, demonstrated that AFC, on average, scored better for first impressions. Many mothers attributed to the manner in which text was formatted, as well as the colour and images. Both AFC and SSN were considered easy to understand, however, despite being identical, participants indicated that the information on AFC was easier to read as it appeared to be more concise.

During Questionnaire Completion

All participants were computer-literate and completed the questionnaire with minimal difficulties. The main difficulty was based more upon the multimedia device that was used to distribute the questionnaires, as many mothers had not previously used a tablet device. Participants felt the instructions were clear, however some parents did feel that some questions were repetitive and that it was difficult to distinguish the difference between some questions in the LRSQ portion of the questionnaire.

There were no other significant concerns in comprehending questions, and there were no specific concerns with the terminology used in the questionnaire. Many participants responded positively to help buttons, which were used for further clarification of questions. Some of the mothers that the research team interviewed indicated that there was some ambiguity with regards to the wording of some questions. The questionnaire refers to "Your child", however four mothers expressed that they became confused to which child the questionnaire was referring.

Figure 3.4 Question Style Preference



When the presentation and format of the LRSQ Likert scale questions were discussed with mothers, the group were divided as to whether Matrix-type scales or drop-down menus were preferred (Figure 3.4). It was noteworthy that many of the mothers that preferred matrix questions upon further discussion with mothers often did so as they were slightly quicker to complete than drop-down menus. However, during the observation of completion of these questions, researchers were concerned that mothers were completing the matrix without reading the question fully.

After Questionnaire Completion

Participants opinion of AFC were also higher than SSN following the completion of the questionnaire. When discussing the time taken to complete the questionnaire, 14 of the 16 mothers were two of the sixteen mothers felt that the length of survey was unacceptable

After Completion of Questionnaire on both AFC and SSN

Of these mothers interviewed, 10 indicated a preference towards AFC software, and six indicated that they preferred survey completion using SSN. Of the mothers that had selected AFC, 90% attributed their preference to the perceived shorter duration of the questionnaire. This may be attributed to AFC having more advanced conditional branching functions, which automatically omits irrelevant questions based upon earlier responses.

After reviewing recruitment materials

Due to time constraints and fatigue, it was not possible or appropriate to discuss the recruitment material with all participants. However, of the twelve that did see the poster and postcard, all reacted positively, and no mothers had specific negative feedback relating to any component of the design and appearance of the poster or postcard. The cohesive theme of all materials was also acknowledged and appreciated by mothers. Of these 12 mothers, eight recognized QR codes and knew how to use them. However, there were no mothers who indicated that they regularly use QR codes, and there were no mothers who expressed that they would use a QR code to sign up to a study.

3.5.4 Discussion

All the mothers who were interviewed by the research students reacted positively to the concept of the study, and like the initial feasibility study, some expressed disappointment that they could not take part in the LRBCS. It is reassuring that all mothers were competent in using the technology, and the prospect of conducting a birth cohort study primarily using online resources for data collection remains a feasible option in the Liverpool population.

The results from this feasibility study indicate that mothers may prefer completion of the LRBCS questionnaires using AFC. This highlights the benefits of this software, as it

permitted researchers to create a survey that appeared very similar to the proposed design from the original PPI session at LWH in July 2012. The software scored better in feasibility testing, and mothers reported that this software had superior functionality and took less time to complete in comparison to SSN. The content of both questionnaires was identical, thus it is reasonable to conclude that it is the superior technology and customizable appearance of AFC that appeals to mothers. These results indicate that AFC would be a reasonable selection for the research team to host the LRBCS questionnaire.

In addition to aiding the research team to reach a decision about software, this small study also highlighted issues that had not previously been considered, which could be addressed prior to the commencement of recruitment. Some of these issues, particularly the ambiguity surrounding the term “your child” can easily be rectified by slightly altering the wording of the questionnaires. The research team will slightly alter this term by using “your new baby”, “your baby”, “your toddler” and “your child” in questionnaires that correspond to these age groups, which the research team hope will provide sufficient clarification. After careful consideration of feedback and their own observations, the research team concluded that drop-down boxes, as opposed to the matrix style questions would be the most appropriate format for questions, and these may ultimately improve the quality of data.⁽²⁰³⁾

Despite this small feasibility study being informative and providing guidance to the research team, it does have a number of limitations. The most considerable of these limitations is the context and setting in which the questionnaires were completed. Parents will not be supervised during completion of the questionnaires, and the questionnaires in the LRBCS will be completed when a child is four months old as opposed to during the neonatal period. The researchers received minimal negative feedback, which may be attributed to the semi-structured interviews being held face-to-face, thus some parents may feel uncomfortable giving criticism. This is a potential bias in the results of the feasibility study. A further possible source of bias in the results is the relatively small sample size, which may not be representative of the demographics Liverpool population. Researchers must also consider selection bias, as mothers were selected based on likelihood to comply, as opposed to randomly, by midwives. Self-selection bias, whereby only certain types of persons are willing to participate in research, must also be considered

Although the research team will consider the limitations of these sessions, they remain useful and aided the LRBCS research team to tailor all elements of the study to appeal to mothers. The information is also useful as it confirms to an extent that mothers

are willing to complete online questionnaires about their children, and that the questionnaire used in the LRBCS is easy to comprehend.

3.6 Preparation for Recruitment

3.6.1 Request for Support

The commencement of recruitment would signify the LRBCS reaching its third phase. Prior to this transition, it was necessary for the research team to finalise and organise the printing of recruitment materials, in addition to building all ten questionnaires that would be used in the LRBCS, and additionally scheduling email invitations and reminders for mothers. In order to implement these tasks, the research team needed to secure funding for these various materials. This was not possible prior to this stage, as the costing could not be calculated before determining the survey software.

To apply for funding, the research team created a Request for Support document that briefly outlined the rationale, objectives and methods of the LRBCS, and explained the necessity of appropriate software for survey distribution and hosting, as well as recruitment material (see appendix 7 for full version of request for support document). The anticipated start-up cost for the LRBCS was predicted to be £486.99, which includes the initial year's subscription to Adobe® FormsCentral, the 10,000 postcards needed for a minimum of 1 year of recruitment and 25,000 email credits. The total cost calculated for 6 years, which includes a 6 year subscription to Adobe® FormsCentral, the 10,000 postcards needed and 25,000 email credits was £1013.96. Conducting the study online ensures the costs of the LRBCS were minimal in comparison to other cohort studies. The research team were not able to estimate the cost of postal questionnaires in this request for support as it was impossible to estimate at this time the proportion of mothers that would opt to receive questionnaires by post.

The finance committee of the Institute of Translational Medicine at the University of Liverpool agreed to purchase the necessary study materials. However, shortly afterwards the LRBCS received a charitable donation from The Friends and Family of Isabella, a patient at Alder Hey Children's Hospital, many of whom work for the North West Ambulance Trust.

3.6.2 Preparation of Questionnaires

Online Questionnaires

After securing funding for the study, both online and postal versions of LRBCS questionnaires were created using Adobe® FormsCentral. The research team created 10 online forms, each representing one of the data collection points, where "Form 1"

corresponded to the initial questionnaire at four months, “Form 2” the first follow up questionnaire at 10 months of age, up to “Form 10” which would be the final questionnaire, sent when the child reached 60 months of age. Each questionnaire was scrutinized by members of the research team and final amendments were made.

Paper Questionnaires

Online questionnaires were reformatted and converted in to printable documents that could be sent by post alongside a covering letter that contained similar information to the invitation emails. A postal consent form was also created in accordance with the guidelines set by the Research Ethic Committee during the application for ethical approval (see Appendix 8 for postal covering letter and consent form).

3.6.3 Preparation and Scheduling of Emails

The research team purchased sufficient email credits for the duration of the study, as purchasing in bulk from MailChimp lowers the price per email. This accounts for a generous response rate of 20% (the predicted response rate for the study is 10%) and an attrition of 0% through the whole study. In the event of more emails being required, these can be purchased at a later date. The research team will re-appraise this number at the end of recruitment, when the total maximum number of emails can be calculated. Purchasing a sufficient amount of credits for the first year would not be economical.

Emails were designed using the same theme as the questionnaires and recruitment materials (see Appendix 9). Researchers proceeded to schedule all invitation emails for the study (Figure 3.5). Each invitation would address the mother personally, and invite her to complete a questionnaire about their named child who was enrolled in the study. Invitation emails also contain the Unique Identification code that was required to complete the questionnaire, and a link to the questionnaire that corresponds to the child’s age. All these emails would be automatically sent based on details held by the LRBCS research team in a secured online database.

Reminder emails have been demonstrated to increase response rates in previous studies, both online and offline. The technology used in the LRBCS permits researchers to schedule up to three reminder questionnaire invitations, which are to be deployed at weekly intervals if a mother has not opened the invitation email, or not clicked on the link to the questionnaire. Birthday emails were also scheduled as previous birth cohort studies have demonstrated that personalised birthday communications are useful in maintaining relationships with cohort members. Birthday emails will also provide a link to an online form where parents can update contact details or sign up to the study newsletter. The

study newsletter will not be scheduled. One newsletter will be deployed quarterly to participants that have expressed interest in receiving the newsletter.

Figure 3.5 LRBCS Email Schedule from Birth to Age Five Years

1. **Immediately after sign up:** Welcome/ Thank you for your interest email – sent immediately after they sign up online, or as soon as we receive their details – will tell them we will be in touch when baby is 4 months old.
2. **4 Months:** Email link to form 1 that contains: consent, further information, demographics, exposures, LRSQ. Also allow them to subscribe to updates from study.
3. **10 Months:** Email link to form 2 that contains: exposures + LRSQ – check no changes to details at end. Also allow them to subscribe to updates from study.
4. **12 Months:** *Happy 1st Birthday email* – congratulate. Check that details have not changed, tell them we will be in touch with another questionnaire in 4 months time. Also allow them to subscribe to updates from study.
5. **16 Months:** Email link to form 3 that contains exposures + LRSQ – check no changes to details at end. Also allow them to subscribe to updates from study.
6. **22 Months:** Email link to form 4 that contains exposures + LRSQ – check no changes to details at end. Also allow them to subscribe to updates from study.
7. **24 Months:** *Happy 2nd Birthday email* – congratulate. Check that details have not changed, tell them we will be in touch with another questionnaire in 4 months time. Also allow them to subscribe to updates from study.
8. **28 Months:** Email link to form 5 that contains exposures + LRSQ – check no changes to details at end. Also allow them to subscribe to updates from study.
9. **34 Months:** Email link to form 6 that contains exposures + LRSQ – check no changes to details at end. Also allow them to subscribe to updates from study.
10. **36 Months:** *Happy 3rd Birthday email* – congratulate. Check that details have not changed, tell them we will be in touch with another questionnaire in 4 months time. Also allow them to subscribe to updates from study.
11. **40 Months:** Email link to form 7 that contains exposures + LRSQ – check no changes to details at end. Also allow them to subscribe to updates from study.
12. **46 Months:** Email link to form 8 that contains exposures + LRSQ – check no changes to details at end. Also allow them to subscribe to updates from study.
13. **48 Months:** *Happy 4th Birthday email* – congratulate. Check that details have not changed, tell them we will be in touch with another questionnaire in 4 months time. Also allow them to subscribe to updates from study.
14. **52 Months:** Email link to form 9 that contains exposures + LRSQ – check no changes to details at end. Also allow them to subscribe to updates from study.
15. **58 Months:** Email link to form 10 that contains exposures + LRSQ – check no changes to details at end. Also allow them to subscribe to updates from study.
16. **60 Months:** *Happy 5th birthday email* – congratulate. Thank them for participation and clarify that there will be no more questionnaires. Ask if they would still like to receive updates for the study.

3.6.4 Printing of Recruitment Material

After a number of minor amendments to the design and content of the recruitment postcard, it was necessary to print these recruitment materials commercially. After receiving quotes and samples from a number of local, national and international printing firms, the research team decided that postcards should be printed on paper that had 300 grams per square meter (gsm) card with a silk finish. Ordering postcards in bulk was most cost effective, thus the research team purchased 10,000 postcards. This number of postcard would be more than sufficient to provide a postcard to each of the 8,000 mothers who give birth at LWH for the planned recruitment of a minimum of 1 year. Postcards were purchased from Saxoprint, a German company, as they offered the most competitive price for the volume of postcards required for one year of recruitment.

3.6.5 Meeting with Senior Midwives

The final preparation prior to commencement of recruitment was the meeting with senior midwives and managers of wards that would be facilitating recruitment at LWH. During this meeting two research students and a senior investigator met with staff and discussed the LRBCS. The research team briefly outlined the rationale and objectives of the study, and explained the recruitment process in detail. Midwives were supportive and indicated that they were willing for postnatal patients to be recruited to the study on their wards, and were also willing to offer feedback on recruitment material, and confirmed that they would be happy to display posters in patient areas. During the meeting, it was decided that the research team would also create information handbooks for staff on participating wards that could be displayed in the staff room to further raise the profile of the study. These packs would contain a letter addressed to ward staff that briefly outlined the study, as well as examples of recruitment material, a brief overview of the study methods and a full version of the study protocol (see appendix 10 for LRBCS midwives document).

3.7 Conclusions

Over a period of three months, the research team were successfully able to transition the LRBCS from a concept to a physical study. Researchers had successfully selected reliable survey and email software that would automatically distribute questionnaires to participants for the duration of the study, with minimal input from the research team. A feasibility study had indicated that the proposed methods of the LRBCS were appropriate, and funding for the study had also been secured, which permitted researchers to purchase all the necessary materials in preparation for the launch of the study.

Chapter 4

Recruitment of infants to the LRBCS

4.1 Introduction

There are a number of different approaches to recruiting participants to population-based birth cohort studies such as the LRBCS. Decisions about the precise strategies for recruitment are usually undertaken with consideration of the availability of staff and resources, the required sample size, or the representation of various demographics of the target population. Large, government funded studies often have specific persons, such as research nurses, that are employed to facilitate recruitment. These studies, such as ALSPAC and Born in Bradford, often report the most impressive recruitment statistics, with upwards of 70% and 80% of eligible participants being enrolled in the studies respectively.^(64, 66)

Other studies have recruited using routine data held in health authority databases, or opportunistically recruited mothers during routine antenatal clinical appointments.^(6, 58-60)

Other studies that aim to identify inequalities within populations have recruited with bias towards certain population groups.⁽¹⁰⁰⁾ One birth cohort study has previously used the internet to facilitate recruitment.⁽¹⁷⁸⁾ The timing of recruitment also varies between studies, with some potential participants being approached for recruitment during antenatal hospital visits as early as nine weeks gestation, whereas other birth cohort studies recruited participants during the neonatal period, and others at age one year.^(6, 64, 204)

The original study protocol for the LRBCS proposed that recruitment for the study would be incorporated in to standard clinical practice at LWH, with recruitment postcards being distributed to all new mothers by midwives or paediatricians, and collected prior to discharge from the hospital. However, after further consideration, the research team decided that this may not be a feasible method of enrolment to the study, as it would solely depend upon the cooperation of staff that are not otherwise involved or affiliated with the LRBCS. Due to the existing workloads of midwives and the high turnover of patients at this large maternity unit, it was decided that recruitment of participants to the LRBCS should therefore be primarily facilitated by the Master of Philosophy (MPhil) students.

Recruitment to the study involves a two-step process (Figure 4.1 LRBCS Recruitment Methods). Mothers will initially complete the recruitment postcard shortly after the birth of their child (Step 1 of consent). This denotes that the mother is interested in participating in the study, and is willing to be contacted by the research team when their child reaches four months old. Complete enrolment in the study occurs when the child reaches four months of age, at the time of the initial questionnaire. Paper consent forms

and information sheets are sent with the initial questionnaire to postal participants. The consent process differs slightly for mothers receiving online questionnaire. The first two screens contain the same information as the information sheet. After reading this information, mothers are asked to tick a box to indicate whether they wish to take part in the study. If they agree to take part, mothers are asked to enter their initials in to an on-screen box to indicate consent for their child to be included in the study. If she indicates that she is no longer interested in participating in the LRBCS, her details will be removed from the email software and she will receive no further communication from the research team. Once the research team has received this completed consent form, a participant is considered recruited and fully enrolled in the study (Step 2 of consent).

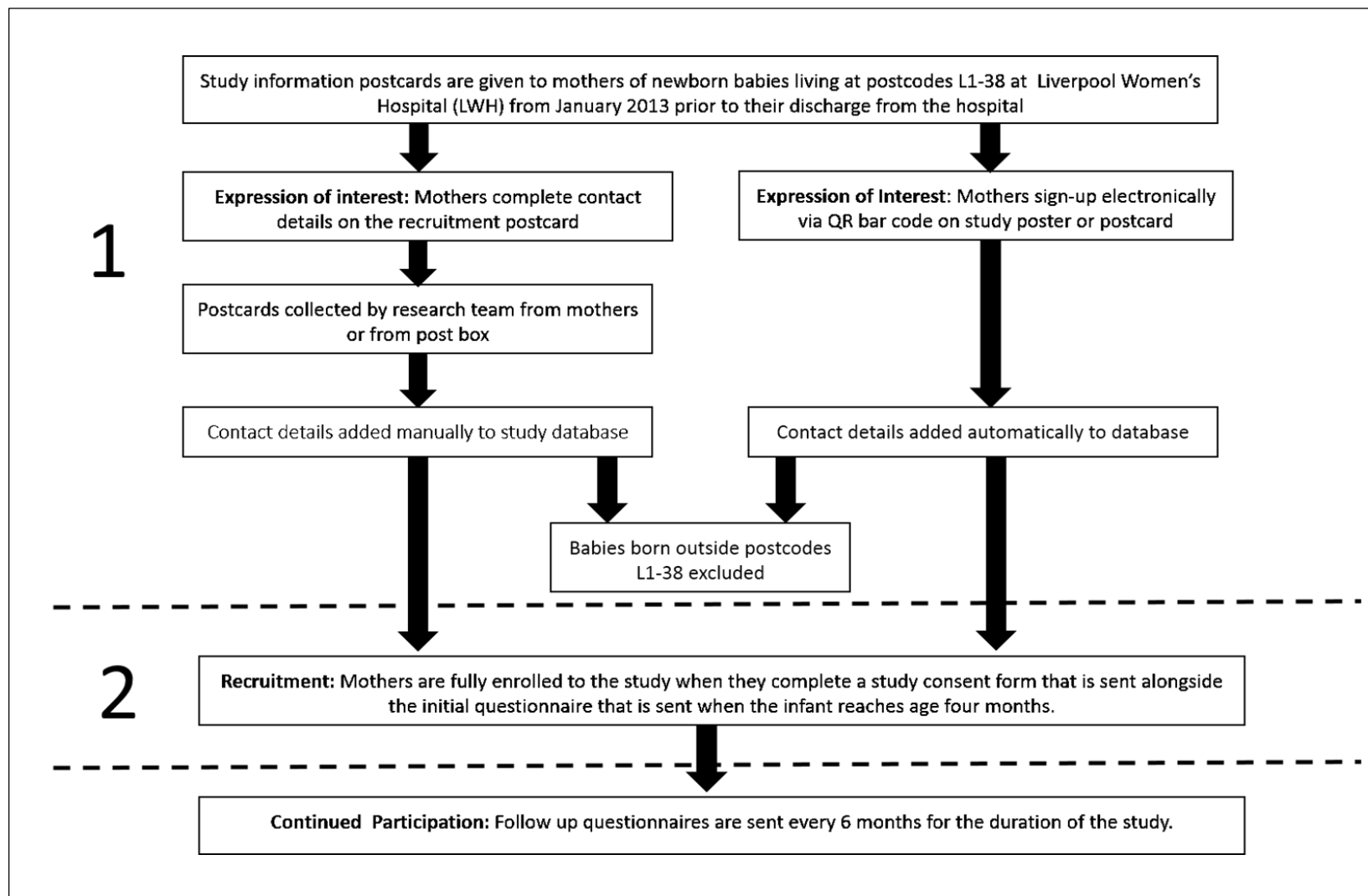
4.2 Piloting Recruitment

In order to determine whether the proposed recruitment methods for the LRBCS were feasible, the research team decided that it was necessary to conduct a four week recruitment pilot at LWH. During this period, researchers aimed to identify the best times of the day to approach patients, with consideration to other ward activities such as ward rounds, meal times and visiting times. As recruitment would primarily be conducted by one research student, the research team also wanted to appraise the number of days per week required in order to meet with a sufficient number of mothers to yield an acceptable number of participants for the study. This four week pilot period would also be used to identify and overcome any other unforeseen circumstances that may hinder recruitment.

This pilot period included three preparatory days, where research students discussed the study with staff on the postnatal wards, distributed and displayed various study materials and started speaking to new mothers about being involved in the study. As the research students had no prior experience of recruiting to a study, during this preparatory period students aimed to establish the best approaches to recruiting new mothers to the study, how much information to provide and the amount of time needed to spend with each patient to provide an appropriate amount of information without bombarding or confusing new mothers.

When planning recruitment, it was also necessary for research students to consider other daily ward activities, such as discharges, ward rounds, and family visiting times. The research students established that LWH operated a strict protected meal time policy, whereby patients could not be approached during the hours of 7.30-8.30am, 12-1pm and 5-6pm. Furthermore, patient visiting times at the hospital were between 2.30-4pm and 6-8pm daily, thus it was inappropriate to recruit some mothers during these times.

Figure 4.1 LRBCS Recruitment Methods



4.2.1 Aims

The aims of the pilot period of recruitment is to establish the most effective method of recruiting to the Liverpool Respiratory Birth Cohort Study in terms of time and the number of patients recruited to the study.

4.2.2 Methods

The four day preparation period for recruitment for the Liverpool Respiratory Birth Cohort Study commenced on January 23rd 2013. Following these preparation days, a four week pilot of recruitment commenced on Monday January 28th 2013. The research team had agreed upon a four week strategy for the pilot, with each week representing a different recruitment pattern (Table 4.1).

Table 4.1 Plan for LRBCS Recruitment Pilot

Week	Week Commencing	Strategy	Times
1	28/1/13	5 Full days (Monday-Friday)	9.30-4.30
2	4/2/13	5 Mornings (Monday-Saturday)	9.30-12
3	11/2/13	4 Alternate Full Days (Monday-Sunday)	9.30-4.30
4	18/2/13	7 Full days (Monday-Sunday)	9.30-4.30

4.2.2.1 Postnatal Wards

During the times indicated in Table 4.1, a research student would endeavour to see all previously unseen postnatal patients at the hospital. During the previous feasibility studies, the research students had noted that patients would often see midwives between 8.30-9.30am, and many others were asleep, thus it was decided that it would not be appropriate to commence recruitment prior to 9.30am. Each day would commence with the research student attending postnatal wards (Matbase ward, Jeffcoate Ward and the Midwife Lead Unit), and obtaining lists of all patients from Ward Clerks, and then identifying all newly delivered mothers. Wherever possible, the research student would identify which patients met all LRBCS eligibility criteria, and removed these patients from the list. Patients living outside of the study catchment area of postcodes L1-L38 were identified by the addresses recorded in their hospital notes. Mothers who could not speak English were identified when it had been written in their notes that they required an interpreter.

After removing ineligible mothers from the list, the research student would then proceed speak to the Midwife that was managing the ward, and confirm whether it was appropriate to speak to all of the remaining mothers on the list. This was an essential step in maintaining excellent relationships with ward staff. This was also the only way to identify mothers of children that were going to be taken in to the care of local authorities, those

patients who had suffered from a neonatal loss or stillbirth, or those that were upset or not suitable to be approached for any other reason.

After finalising the list, the research student would commence recruitment. Wherever possible, the research student would endeavour to see every eligible mother each day, up until the time specific in the planned recruitment strategy. The research student would approach mothers on an individual basis, and clarify their role. If the mother was happy to proceed, the research student provided a brief explanation of the study, including the nature and purpose for the study, as well as the rationale for a longitudinal study of preschool children in Liverpool. The research student would then explain that the study involves a questionnaire sent twice a year by email or by post, commencing when their child reached age four months and continuing until their child was five years old. It was stated that there would be no direct benefits for mothers or their children for participating in the LRBCS, but that the study could benefit future generations of children in Liverpool. The research student would then address any questions that the mother may have. If the mother then indicated that she would be interested in participating in the study, the research student would provide a recruitment postcard which the mother could complete in order to register her interest in the study with the research team. If the mother was unsure or declined, the research student would thank her for her time, and offer to leave a recruitment postcard with her, which she could complete and post in the ward's collection box if she later changed her mind. Following completion of the recruitment postcard, the research student would thank the mother for her time, and inform her that she would receive an email in approximately 1 week to confirm that the research team had received her details. She was also informed that she would then receive subsequent communication when her child reached age 4 months, which would invite her to consent and fully participate in the study.

4.2.2.2 Neonatal Unit

Parents of eligible infants that had been admitted to the Neonatal unit were also invited to participate in the study. Children admitted to the Neonatal unit may be receiving therapy for one or a number of reasons, including prematurity, low birth weight, infections or other prenatal or perinatal complications. It was therefore necessary for the research student to consider these factors when approaching the mothers of unwell children during their routine stay at one of LWH's postnatal wards, and confirm with the midwives overseeing these mothers' care that it would be appropriate to approach these women.

Mothers that had not been seen by a member of the research team, or had previously declined to participate, were given a further opportunity to participate prior to their child's discharge from the neonatal unit. Nursing staff would provide recruitment postcards to the mothers of all eligible children. If a mother now wished to register her interest in the study, she could complete the postcard and hand it back to a staff member who would deposit the postcard in the collection box situated on the ward.

4.2.2.3 Cystic Fibrosis

In addition to the core recruitment strategy of the study, parents of children diagnosed with cystic fibrosis (CF) as a result of the NHS national newborn screening programme were invited to participate during an initial consultation with a respiratory physician. However, to be accepted in to the study, it was necessary for these children to meet the recruitment criteria, and to be recruited prior to the deployment of the initial questionnaire at four months of age. Therefore, these children had to be domiciled within eligible postcodes and born at Liverpool Women's Hospital, and be the offspring of English-speaking parents.

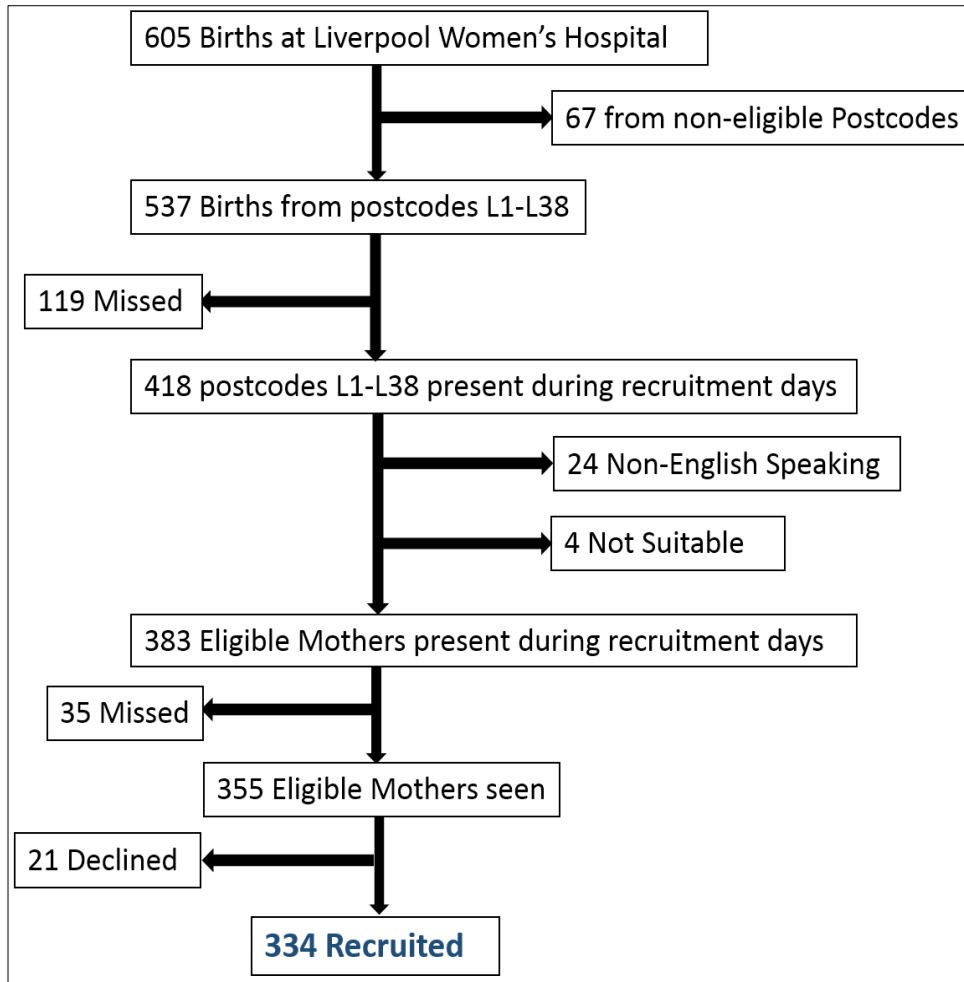
4.2.3 Results

A total of 334 mothers on postnatal wards at Liverpool Women's Hospital expressed interest in participating in the LRBCS during the four week pilot period. All of these mothers were personally recruited by the research student, and there were no expression of interest cards deposited in the collection boxes on the postnatal wards. However, there were three expression of interest cards that had been completed by mothers of children on the neonatal unit. All expressions of interest that were received by the research team during the pilot recruitment period were as the result of a mother completing the physical postcard; no parents expressed interest by completing the online form accessible by the QR code. In addition to these 337 mothers, a further 34 mothers that had expressed interest during the three preparation days prior to the pilot, and two mothers of infants with cystic fibrosis had also provided contact details to the research team. At the end of the pilot period, the research team had contact details of 371 mothers who were interested in participating in the study.

There was a total of 605 infants born at Liverpool Women's Hospital during the four week pilot period. Of these, 537 were born to mothers living in eligible postcodes for participation in the LRBCS. However, only 418 of these eligible mothers were available to be seen whilst the research student was present on the wards. There were approximately 24 births to mothers that were unable to speak sufficient English to consent to participation in the study, and midwives requested that four mothers were not seen by the research

student for a number of social or personal issues. Therefore, the research student met 355 eligible mothers during the pilot period, and successfully obtained expressions of interest from 334 of these (see Figure 4.2 and Table 4.2). The average recruitment rate for the four week period was approximately 65% of eligible births [95% CI, range = 60.87% to 69.13%]

Figure 4.2 Recruitment Flow Chart



Week 1 – 5 Full days of recruitment

The first week of piloting recruitment involved five full working days of recruitment at Liverpool Women's Hospital. A total of 142 children were born at the hospital during this week; 104 during the 5 days that the research student was recruiting, and a further 38 during the weekend. Of these 142 children, 121 were domiciled within eligible postcodes. The research student was able to see 77 eligible mothers, nine of which declined and a further three mothers could not speak sufficient English to consent to participate in the study. The research team was able to recruit 68 eligible mothers to the study during the

first week of recruitment, thus the recruitment rate of eligible infants for 5 full working days of recruitment was 68 out of 118, or 58% [95% CI, range 49.09% to 66.91%].

Week 2- 6 Mornings of Recruitment

During the second week of the recruitment pilot, the research student would only recruit mothers during the morning. Recruitment for the day would thus stop when patients received their lunch time meals at 12pm, irrespective of whether the research student had seen all the postnatal women. During the second week, 144 of the 166 births at the hospital were to mothers living in postcodes that were eligible for the LRBCS. Six mothers from eligible postcodes were not able to speak English, and it was not appropriate to speak to one mother as her child was under the care of the local authorities. The research student met with 94 of the 137 suitable mothers during the six mornings of recruitment, 89 of whom expressed interest in participating, thus the recruitment rate was 65% [95% CI, range 57.01% to 72.99%]

Week 3 – Alternate Days

The third week of the recruitment pilot consisted of the research student attending the hospital on four alternate days of the week, and completing a full day of recruitment. There were 144 births, 12 of which from outside the LRBCS catchment and eight were children of non-English speaking mothers. The research team was able to speak to 81 mothers over the four days, five of which did not wish to participate in the study. The research student was able to see some of the mothers that had delivered the previous day, thus the recruitment rate for the third week was therefore 61% [95% CI, range 52.42% to 69.58%]

Week 4- 7 Full Days

The fourth week of the recruitment pilot was the most rigorous. During the final week, the research student was present on post natal ward from 9.30-4.30pm on seven consecutive days. During week four, there were 153 births at the hospital, 140 of which were to mothers living within eligible postcodes. A further six mothers were not eligible for participation due to language, and the mothers of three infants were not approached for participation due to ongoing social difficulties. The research student successfully met with 103 of the 131 eligible mothers, and 101 of which expressed interest in participating. Therefore, the recruitment rate for the fourth week of piloting recruitment was 78% [95% CI, range 70.91% to 85.09%].

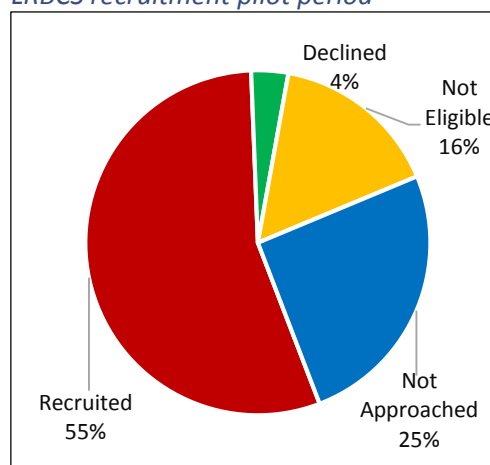
Table 4.2 Weekly Summaries of Recruitment Data

Week	Total Births	Births from eligible	Available to see	Not eligible: Language	Not eligible: other reason	Seen by Researcher	Declined	Recruited	Recruitment Rate (%)	Range for the True Population Proportion (%) [95%CI]
1	142	121	82	4	0	77	9	68	58	49.09-66.91
2	166	144	113	6	1	94	5	89	65	57.01-72.99
3	144	132	92	8	0	81	5	76	61	52.42-69.58
4	153	140	131	6	3	103	2	101	78	70.01-85.09
Total	605	537	418	24	4	355	21	334	65	60.87-69.13

4.2.4 Discussion

The LRBCS research team obtained expressions of interest from the mothers of 334 eligible infants born at Liverpool Women's Hospital during the recruitment period. Of all the 605 births that occurred at the hospital during the four week pilot, 16% (n=96) were not eligible, 4% (n=21) declined to participate, and 55% (n=334) expressed interest in the study (Figure 4.3). Therefore, the research team were not able to approach 25% (n=154) of eligible births occurring at Liverpool Women's Hospital. By the end of these four weeks, the cumulative total of expressions of interest in the study was 371 (see Figure 4.4). The research team were able to approach almost 70% of mothers that were eligible for participation in the LRBCS. Of the eligible mothers that were approached by the research team, approximately 93% [95% CI, range 90.35% to 95.65%] completed and returned expression of interest postcards.

From this data, it is reasonable to infer that the concept of the Liverpool Respiratory Birth Cohort Study is attractive to parents, as a large proportion of eligible mothers who were approached for participation expressed interest in the study. The results from the recruitment pilot demonstrate that the greatest obstacle to affect recruitment to the study will be accessing mothers. Even when employing a maximum recruitment strategy (Week 4), the research team were not able to approach 22% [95% CI, range 14.91% to 29.09%] of eligible mothers, and during the whole

Figure 4.3 Breakdown of births during the LRBCS recruitment pilot period

pilot, over a quarter of all eligible mothers were missed (Figure 4.5). This may be attributed to a number of contributing factors, including night-time births, the short discharge times associated with uncomplicated births at the hospital. Additionally, researchers were not permitted to speak to some mothers, and the presence of visitors also limits recruitment during the afternoons.

In addition to setting the baselines which the research team could use to forecast recruitment, data from the recruitment pilot also permitted researchers to appraise the various recruitment strategies that were trialled. As anticipated, the most successful strategy was the fourth week, during which a research student was present on the ward for seven consecutive full days. During this week, the research student was able to recruit 78% (n=101) of all eligible births, which, despite being a considerably higher figure than previous weeks, there was overlap in the confidence intervals for this week and week 2 (6 mornings). Therefore, despite some variation in the recruitment rates for the four weeks of recruitment, due to the overlap in confidence intervals, it is difficult to determine whether any one week's strategy was significantly more efficient than others (see figure 4.6). Furthermore, in addition to appraising the "best strategy", it is necessary to consider the feasibility of continuing each of the four strategies beyond the pilot phase, as recruitment could only be facilitated by one research student, who would also require time to carry out other administrative duties. Thus, it was decided by the research team that the number of hours or days recruited did not have a significant effect upon recruitment rate. As a consequence of this, the research team decided that it would be more appropriate to tailor the recruitment times and days to suit the person that was recruiting.

Figure 4.4 Cumulative Total of Expressions of Interest during recruitment Pilot

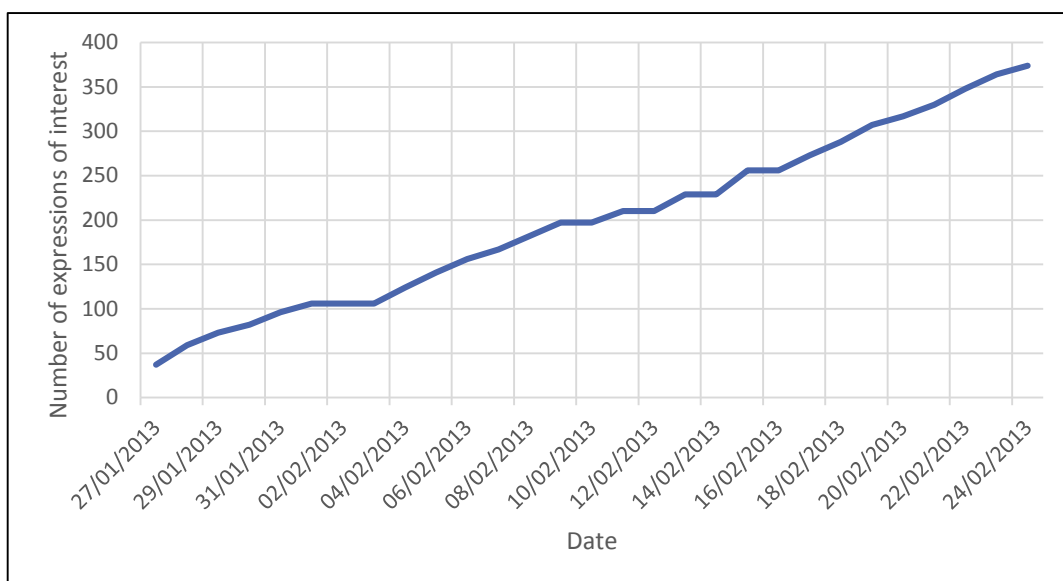


Figure 4.6 Weekly recruitment Rates for the LRBCS recruitment pilot

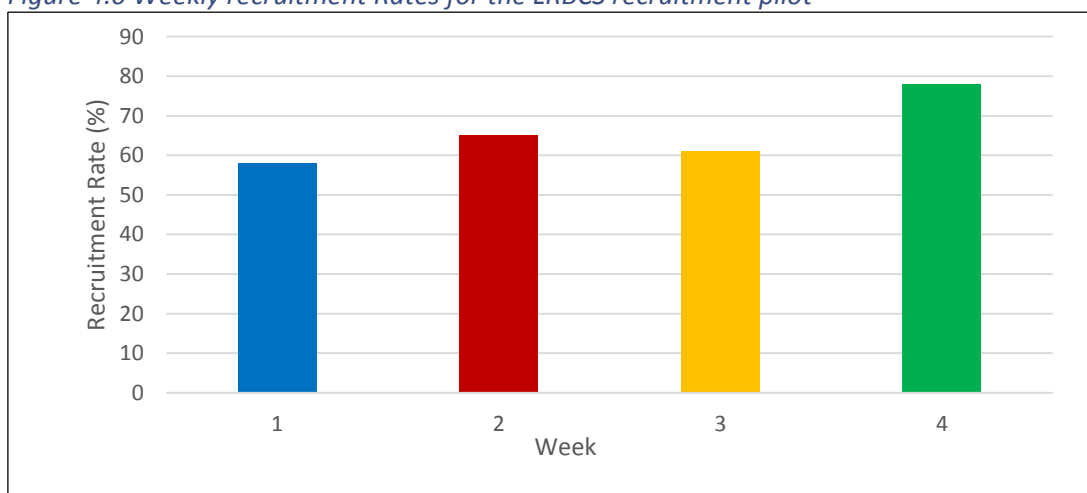
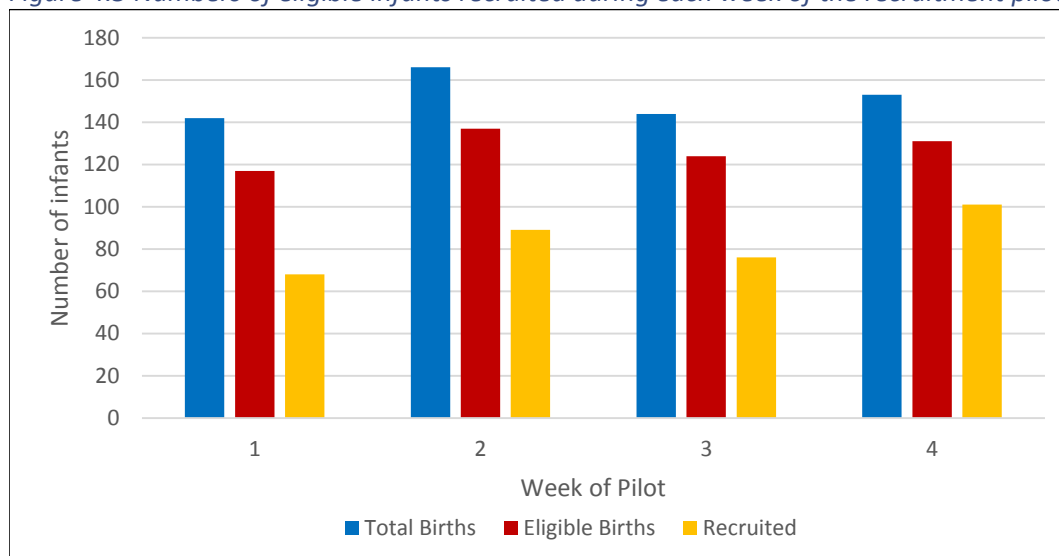


Figure 4.5 Numbers of eligible infants recruited during each week of the recruitment pilot



LRBCS Pilot Profile

In addition to appraising recruitment rates, data from the LRBCS pilot could also be used to create a profile of some characteristics of the 334 mothers who had expressed interest in the study. An important characteristic that needed to be appraised was whether the group had socioeconomic demographics that were representative of Liverpool population, as this was one of the study's key areas of interest. Furthermore, it was desirable to calculate the number of mothers opting for online questionnaires, to further ascertain the feasibility of primarily conducting the LRBCS using the internet. It was also possible to profile other characteristics, including ethnicity and the geographical representation of participants.

Therefore, an analysis of the data available from the mothers who had expressed interest in the study during the pilot was conducted, and have been described in greater detail elsewhere.⁽²⁰⁵⁾ It is of significance that this preliminary analysis of the pilot group demonstrated that the mothers who expressed interest in the LRBCS had similar Indices of Multiple Deprivation (IMD) scores to all mothers who delivered at Liverpool Women's Hospital during the pilot period. IMD scores are derived from qualitative data collected by the UK government about various aspects of deprivation, including income, employment, health deprivation and disability, education skills and training, housing, barriers to services, crime and living environments.⁽²⁰⁶⁾ This is considered to be the most comprehensive measure of deprivations in the UK. Areas in which residents are the most deprived in the context of these aspects are assigned the lowest scores. It can therefore be postulated that the socioeconomic deprivation of mothers expressing interest in the study were representative of the Liverpool population as a whole.

This analysis demonstrated the demographics of the cohort were grossly representative of the Liverpool population. The male to female sex ratio of infants was not significantly different from the national average. The research team had received expressions of interest from the mothers of three sets of twins. The incidence of twin births is approximately 1 in 100, thus with 334 mothers enrolled, this number is accurate. Furthermore, analysis of the ethnicity also demonstrated that the ethnic diversity of mothers that had expressed interest in participating in the study were representative of the Liverpool population. The geographical spread of mothers was satisfactory, however, geocoding of postcodes demonstrated that some postcodes were underrepresented due to their close proximity to other hospitals that offer maternity services.

It was also reassuring to the research team that 78% of mothers that expressed interest in participating in the LRBCS asked to receive communication and questionnaire

invitations by email, and just 22% opting for postal correspondence. This further supports the decision to conduct the LRBCS primarily online.

Therefore, early analyses of the pilot group demonstrated that mothers expressing interest in the study during the recruitment pilot were relatively representative of the Liverpool population in a number of domains. However, the sample size is relatively small, thus the results of the pilot may not be completely reliable. It will be necessary for the research team to continuously monitor the demographics of the cohort throughout the duration of the study to ensure that the sample remains representative, and make the appropriate corrections if not.

4.2.5 Conclusions

Final Recruitment Strategy

Following the four week pilot, the research team met and discussed the results of the pilot. It was decided that although a seven day recruitment strategy would be optimal, as this strategy achieved recruitment rates similar to larger, well-funded birth cohort studies. ^(64, 66) However, it was decided that this strategy would not be a feasible long-term recruitment strategy for the LRBCS. This decision was reached by the research team because the one research student facilitating recruitment would also be responsible for managing study databases, administering postal questionnaires, overseeing online responses and responding to telephone and email queries from parents.

The research team concluded from the pilot results that four full days of recruitment could be sufficient to yield an acceptable number of expressions of interest. Recruitment figures for the third pilot week (recruitment on alternate days) demonstrated that it was possible to “catch up” with the mothers that had given birth during the previous day, and that similar amounts of mothers were missed regardless of the recruitment strategy (with the exception of four full days). The research team therefore decided to trial one further recruitment pattern, where the research student would recruit on four weekdays (Monday, Tuesday, Thursday and Fridays), and could use one day in the middle of the week to perform the study’s various administrative tasks.

This strategy was tested during the week commencing the 11th of March 2013, during which there were 145 births at the hospital. 133 of these births were to mothers living within the eligible postcodes for the LRBCS. A further six mothers living within postcodes L1-L38 were not eligible as they could not speak sufficient English to communicate with the research student, and two infants could not be included in the study as they were under the care of local authorities. Of the 124 eligible births between the 11th

and 17th of March, the research student met with 85 mothers. Of these, 83 expressed interest in participating in the LRBCS. Therefore, the recruitment rate for this strategy was 69%. Thus, the research team agreed that this recruitment pattern was effective, and the research student should proceed to meet mothers at LWH according to this.

Strengths and Benefits of conducting a recruitment pilot for the LRBCS

There are number of benefits gained from piloting recruitment for a birth cohort study to ensure feasibility prior to fully implementing strategies. This four week period permitted the research student to identify the best approaches to recruitment and to develop a plausible recruitment strategy for the study for the particular maternity hospital that facilitated recruitment. The pilot was conducted on all of the postnatal wards that would be facilitating recruitment to the study, thus it is reasonable to assume that the data from the pilot is reliable. The research team were satisfied with the recruitment rates, particularly as only a small minority of mothers declined to participate.

Limitations of the recruitment pilot

Although the data collected during this recruitment pilot will be useful for researchers, and guide the research team in planning future recruitment to the LRBCS, the recruitment pilot also has some limitations that must be considered. Firstly, despite having the preparation days prior to commencing the pilot, the inexperience of the research student may have affected recruitment during the pilot period. This may account for the lowest recruitment rates of the pilot occurring during the first week. Furthermore, it was not possible for the research team to calculate the precise recruitment rate of eligible births to the LRBCS during the pilot period. Some of those mothers who were missed, or discharged during the night or other periods when the research student was not recruiting, may not be English-speaking, or may not have been eligible for other reasons.

Furthermore, although a high number of mothers expressed interest in the study, this does not correspond to full enrolment, as mothers are not fully consented for the study until their child reaches four months. Therefore, despite the sample size being satisfactory for the pilot, the research team anticipates a large dropout at four months due to non-response. Mothers that do not respond at four months have not consented, thus cannot be contacted again by the research team.

4.3 Further Recruitment

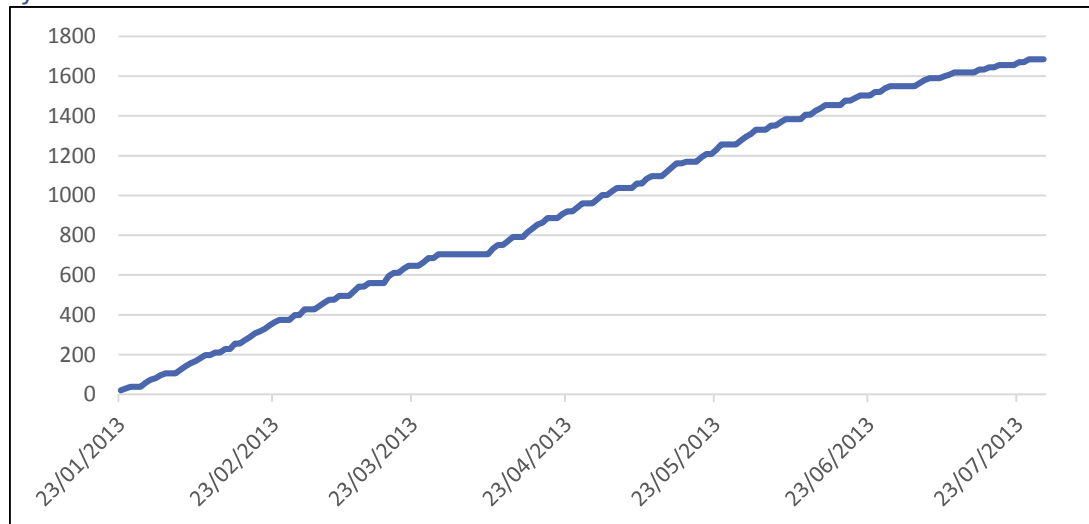
After establishing the most efficient recruitment strategy for the study, the research student continued to meet with mothers at LWH in order to obtain expressions of interest for participation in the LRBCS. This research student continued to recruit up until the 31st of

May 2013, however there was a one week recruitment break at the beginning of April due to the study team not having anyone available to recruit. Recruitment was continued by a volunteer during the months of June and July. The study will undergo a recruitment break during the month of August, and it will recommence in early September when a new research student joins the LRBCS team.

The research team has now successfully obtained expressions of interest from the mothers of 1,685 eligible infants. Of these, eight expressions of interest have been obtained from postcards deposited in the collection box on the neonatal unit, one postcard as deposited in the box on the Midwife Lead Unit, and one mother has expressed interest in participating in the LRBCS by completing the online form accessed by scanning the QR code using a smartphone. Additionally, there are two infants with cystic fibrosis who met all eligibility criteria that were recruited by a respiratory physician that is a member of the research team. Therefore, over 99% of mothers that expressed interest in the study did so as a result of personally meeting a member of the research team during their postnatal stay at Liverpool Women's Hospital. This supports the evidence from previous studies, that adopting a personal approach to recruitment is essential to ensure the successful enrolment of a large proportion of eligible infants to a population-based birth cohort study.

(64-66)

Figure 4.7 Cumulative Total of expressions of interest in the LRBCS after the first six months of recruitment



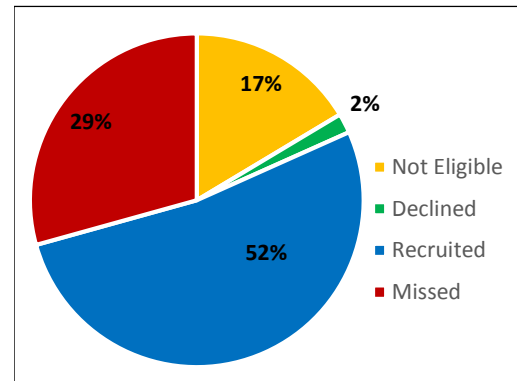
Since recruitment commenced in January 2013, there have been 3,218 live births at Liverpool Women's Hospital. Of these, 2,868 infants were born to mothers domiciled within postcodes eligible for participating in the LRBCS. The research student identified that in addition to 24 mothers identified in the pilot, at least a further 127 mothers were not eligible to participate in the study as they were not able to speak English. There were 27

mothers that were not eligible or able to participate due to social problems, including approximately 11 children who were under the care of local authorities. Therefore there were 2,690 eligible births during this six month period. 62 mothers have declined to participate in the study. At present, the research team have obtained expression of interest in participation from the mothers of 1,685 children (Figure 4.7). Therefore, the research team had failed to see 943 potential participants during this six month period.

4.3.1 Recruitment Rates

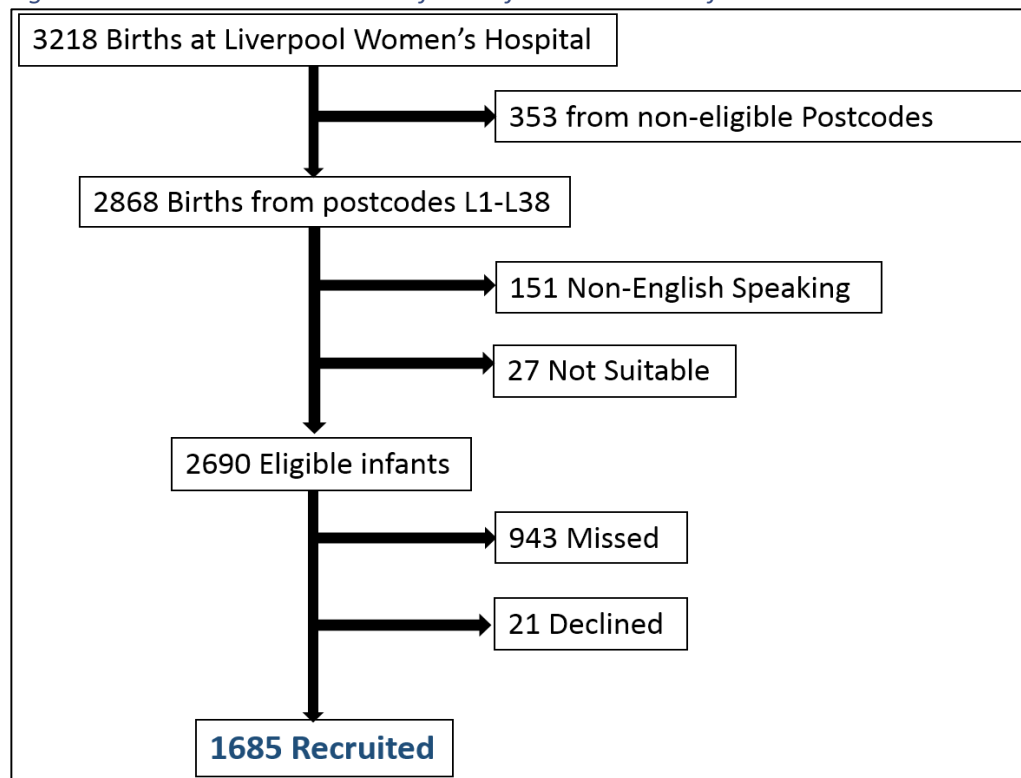
The research team estimate that approximately 84% of births at LWH are eligible for participation in the LRBCS (see Figure 4.8). The research student obtained expressions of interest of approximately 63% of eligible mothers during the first six months of recruitment for the LRBCS, and just 2% of mothers declined to participate.

Figure 4.8 Proportion of eligible mothers That were seen and recruited to the LRBCS



The research team are satisfied with this number, however it is essential to consider that only a fraction of these mothers are anticipated to fully enrol in the study by completing the consent form alongside the initial questionnaire at four months.

Figure 4.9 Recruitment Flow Chart for the first six months of the LRBCS



4.3.2 Preference of Online questionnaires

Online questionnaires are considered to be an important element of the LRBCS study design. During feasibility testing, almost all mothers indicated that they would prefer to complete questionnaires about their child's health online. Furthermore, the majority of mothers that expressed interest in the study during the recruitment pilot also indicated that they would prefer to receive communications and questionnaires by email, with just 22% opting to receive paper versions by post. However, over the following five months the number of participants preferring the postal option increased. At the end of the initial six month period of recruitment, two thirds of mothers had indicated a preference for online questionnaires, whereas one third desired to be contacted by traditional postal methods. However, when appraising these preferences on a month-by-month basis, a significant change in the ratio of online to postal participants occurred during the months of June and July (Table 4.3). This coincides with a new member of the research team assuming the responsibility for recruitment, thus indicating that these figures may have changed as a result in this change in recruitment.

Table 4.3 Percentages of mothers requesting online versus postal communication from the LRBCS study team

Month	Online (%)	Postal (%)
Pilot	78	22
March	74	26
April	69	31
May	76	24
June	46	54
July	54	46
6 month Mean	66	34

4.3.3 Geographical Representation

Analysis of pilot data from the LRBCS demonstrated that the geographical representation of mothers who had expressed interest in participating in the study was an accurate representation of the distribution of the population within Liverpool postcodes, with some exceptions. A similar analysis was performed using the first half of postcodes provided by mothers on the expression of interest cards during the first six months of recruitment to the study (n=1685). These were geocoded using a batch geocoding tool, which permits researchers to visualize the geographical spread of participants across postcodes L1-L38. This data was compared to routine data provided by LWH, which the research team could then use to compare the number of births per postcode area with the number of

expressions per each area. In order to determine whether these numbers corresponded to each other, and to identify whether certain postcodes were being overrepresented in the study, these figures were then converted in to percentages (see Figures 4.10 and 4.11).

Figure 4.10 Number of women domiciled in eligible postcodes that expressed interest in the study compared to all women delivering at LWH

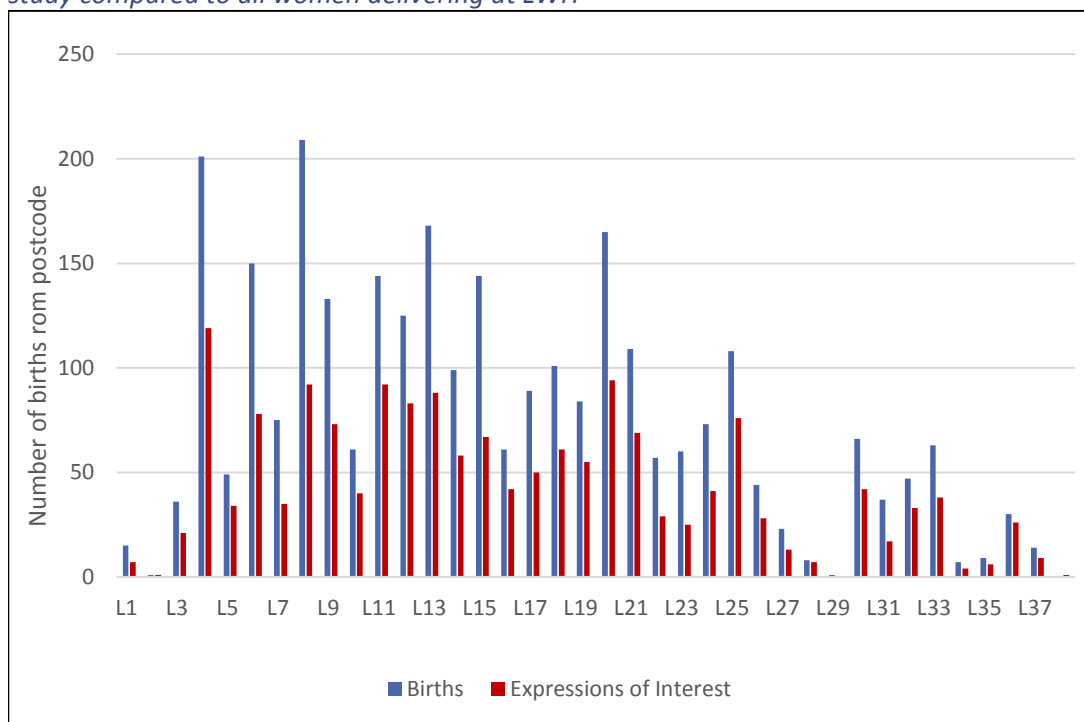
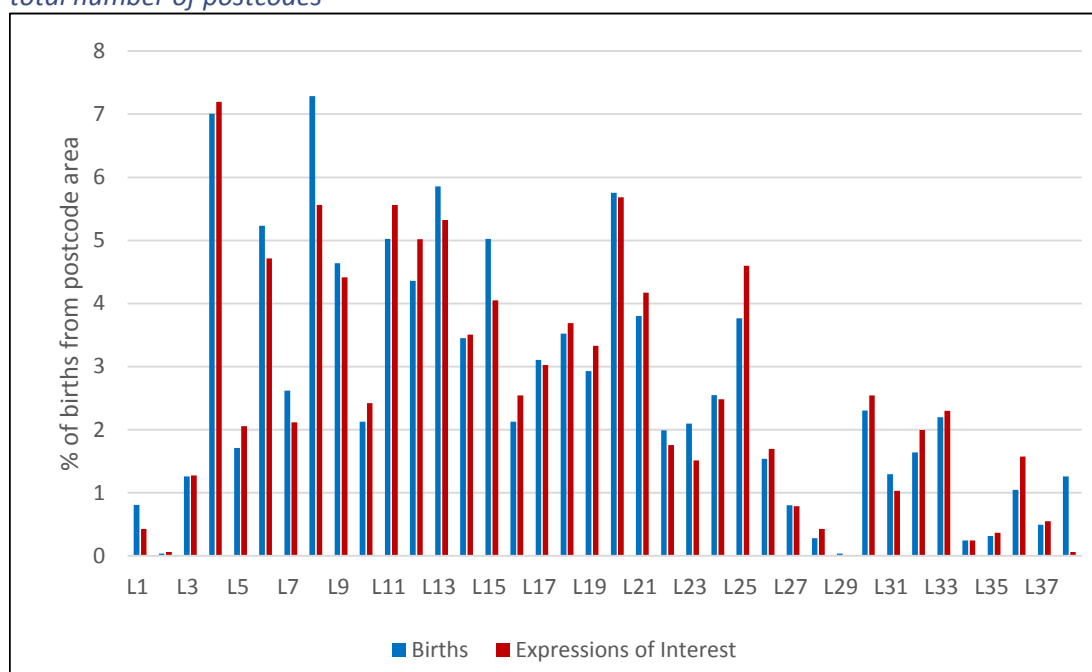


Figure 4.11 Representation of eligible postcodes versus expressions of interest as a % of the total number of postcodes

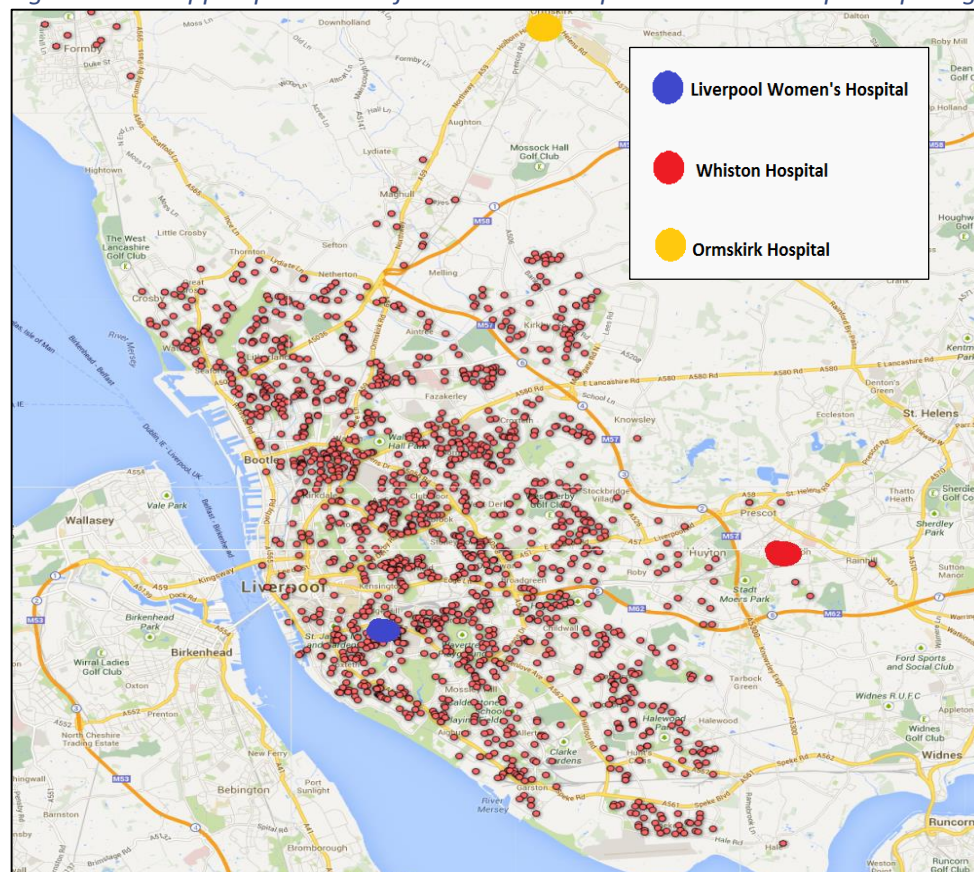


These graphs demonstrate that most Liverpool postcode areas are accurately represented by the mothers who have expressed interest in the study. However, the postcode areas of L8 and L15 do appear to be underrepresented in the expression of interest group. This is of significance as both of these postcode areas have average IMD scores in the 5th quintile, thus these areas are home to some of the most deprived people in England.

Overrepresentation also occurred, with higher than anticipated percentages of expressions of interest coming from L25. This is also significant, as the average IMD score for this postcode area is in the 4th quintile, and thus are the less deprived than two thirds of the city's population. This evidence could begin to demonstrate that there may be a bias towards infants of more affluent parents being overrepresented in the study, a bias which has been reported by other birth cohort studies. ^(178, 207) The deprivation scores of all mothers in comparison to those who expressed interest are discussed in depth in Chapter 5.

When visualised on a map (see Figure 4.12), the geographical spread of the mothers who expressed interest in the study demonstrates that a bias may also exist towards mothers living within closer proximity to Liverpool Women's Hospital. The map

Figure 4.12 Mapped postcodes of mothers who expressed interest in participating in the LRBCS.



demonstrates that the LRBCS recruited less mothers from the areas surrounding Whiston Hospital and Ormskirk hospitals, as these both offer maternity services to the surrounding areas.

4.3.4 Ethnicity

Analysis of the ethnicity of the pilot group demonstrated that the ethnic diversity of infants that had been fully recruited to the LRBCS was similar to that of the general Liverpool population. However, the ethnicity of infants that have been recruited to the study demonstrates that the White British population may be overrepresented in the cohort, with underrepresentation of children for Asian or Black ethnic backgrounds. This is discussed in further detail in chapter 5 of this thesis.

4.3.5 Maternal Age

Maternal age is an important factor that needs to be considered when determining whether the mothers expressing interest in the LRBCS representative of all mothers are delivering at Liverpool Women's Hospital. This is of particular significance as other birth cohort studies have demonstrated that a self-selection bias towards older mothers sometimes occurs in these studies⁽¹⁷⁸⁾ This information is collected by the first questionnaire, however the research team are currently in the process of retrospectively obtaining this information about mothers who expressed interest in the study, as the demographics of these mothers may differ from those completing questionnaires.

4.4 Recruitment of Infants from the Neonatal Unit

The neonatal unit at LWH cares for approximately 1,000 premature babies annually. A number of these infants are born to mothers living across Merseyside, Cheshire, North Wales and other areas, and thus many are not eligible for participation in the LRBCS. However, the research team felt it was essential to ensure that the study did enrol eligible infants who had been cared for at the unit in order to investigate the effects of prematurity upon respiratory symptoms, and also to understand the relationship of prematurity with other risk factors and demographics in the context of long term respiratory health.

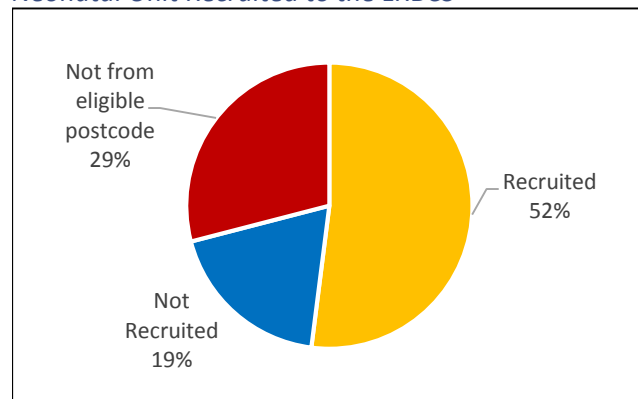
The research team were concerned initially that only three postcards had been deposited in the collection box at the unit. Following conversations with the relevant members of staff, the research team discovered that the majority of eligible mothers were being approached by the research student whilst staying on the hospital's postnatal wards, and thus eligible premature infants were not being missed. However, the research team felt it was necessary to appraise the precise number of these infants that were being enrolled

to the study, to ensure that there was an accurate representation of premature infants in the cohort.

The research team were able to obtain discharge data from the neonatal unit for a 12 week period. Children from eligible postcodes were identified from the neonatal unit list, and compared to the database of study participant contact details to determine whether the mothers of these children had expressed interest in the study. It was found that over the twelve weeks, there were 248 infants discharged from the unit (Figure 4.13).

Of these, 72 were not eligible to participate in the study as they were born to mothers living in postcodes outside of L1-L38. The research team had obtained expression of interest from mothers of 129 of the 176 eligible mothers, thus the recruitment rate for the unit was 73%. This rate is higher

Figure 4.13 Proportion of infants discharged from LWH Neonatal Unit Recruited to the LRBCS



recruitment rate than the study recruitment rate of 63%. This difference may be attributed to mothers of premature infants staying at the hospital for longer than the mothers of healthy 47 mothers were not recruited to the study, however, this does not necessarily mean that they were not approached for participation. A proportion of these may not have been able to speak English, and furthermore this number does not account for mothers who were not eligible for social reasons, those who the research student was advised not see by midwives, and mothers that were approach for participation but declined. Children that were cared for by the neonatal unit accounted for 16% of all expressions of interest received by the research team during this 12 week period.

4.5 Conclusion

The recruitment strategy for the Liverpool Respiratory Birth Cohort study appears to an effective method of accessing mothers of eligible infants and obtaining expressions of interest. This approach is therefore suitable for recruiting infants to a population-based birth cohort in the city of Liverpool. The LRBCS has also demonstrated that passive recruitment, by displaying recruitment materials alone, or relying on staff members to opportunistically recruit would not be a feasible strategy for recruiting a significant number

of mothers to a birth cohort study. This is supported by evidence from a number of other studies conducted in the UK and Europe.^(64, 65, 70, 178)

The research team realised during the pilot that the greatest factor limiting recruitment to the LRBCS was seeing all the mothers. A proportion of women giving birth at LWH are discharged within 6 hours of delivery, and additionally, it was not feasible for the research student to recruit during the weekend as recruitment is facilitated by just one research student who also has other administrative duties to complete. Ultimately, this means that it is unavoidable that some mothers are not seen by the research student.

Despite these factors that restricted recruitment, 63% of eligible mothers, or 99% of those mothers approached, expressed interest in participating in the LRBCS. Just 1% of mothers declined to participate during the first step of enrolment to the study. The limited data obtained by the research team suggests that the demographics of mothers who have registered interest in the study are a fairly accurate representation of mothers in Liverpool. Results from the initial questionnaires will demonstrate whether mothers that fully enrol in the study are also a representative sample, as previous birth cohort studies have demonstrated that a self-selection bias exists towards children born to older, more educated parents that live in more affluent areas.⁽¹⁷⁸⁾

Recruitment will continue for at least 12 months from the end of the pilot. However the research team hope that as the study grows and progresses it will attract substantial funding that will permit recruitment to continue beyond this. To achieve maximum recruitment, the study would require at least one research nurse to be employed, whose sole role would be to meet mothers and recruit participants.

Recruitment to the study appears to be subjective, and it may be affected by a number of factors, including the person who is recruiting. This is demonstrated by the reduction in the number of women declining to participate as the student facilitating recruitment became more competent. Further evidence is the reduction of the recruitment rate that was observed when the student that was initially recruiting the study was replaced by a volunteer. It is also of significance that, despite not being involved with recruitment, staff on postnatal wards played a crucial role in recruitment, and maintaining excellent relationships with managers, ward clerks and midwives is essential for the future success of recruitment to the study.

Chapter 5

Preliminary Results from the Initial LRBCS Questionnaire: Symptoms in 2nd through 4th months of life

5.1 Introduction

In May 2013, the Liverpool Respiratory Birth Cohort Study moved in to its fourth and final phase, in which the research team began to distribute the initial questionnaires for the study. The dataset from the study will be complete following five years of longitudinal follow-up of children that were enrolled in the study by their at age four months. Data will include information about important demographics and exposures that alter the risk of respiratory disease in children, including sex, birth weight, gestation at birth, household tobacco smoke and socioeconomic deprivation. The variables and exposures that can change over time, such as smoking or nursery attendance will be recorded on a six monthly basis. Along with these questions, parents will complete the LRSQ, which collects information about symptoms for the preceding three months. Parents will receive the first questionnaire at age four months, and will continue to receive questionnaires until their child is five years old.

Following five years of follow up, longitudinal data from respondents will be linked. This will allow researchers to gain insight in to the effects of these exposures upon the prevalence and severity of respiratory symptoms in preschool children living in Liverpool. This information will also permit researchers to understand how the relationship between exposures and symptoms changes over time. In order to do this, researchers will perform univariate, multivariate, and linear regression will compare domain scores of the symptoms questionnaire with demographics. Structural equation analysis may also be used to assess any relationship that is found between variables and symptom scores. Furthermore, the research team wish to further assess the validity of the LRSQ as a research tool.

The data for each age group (ages four months, 10 months, 16 months etc.) is stored in separate databases, therefore it will be possible for the research team to perform interim analyses upon the data at various time points. This will allow the research team to identify whether drop-out from the study introduces bias to the sample of mothers and infants participating in the study. If identified, analysis of results will need to be corrected for the overrepresentation or underrepresentation of certain groups within the population.

Furthermore, interim analyses will also permit researchers to continuously monitor trends in the respiratory health of preschool children living in Liverpool.

Therefore, this analysis will not be possible until approximately four months after the final expression of interest has been received by the research team. However, for the purpose of this thesis, it was possible to analyse preliminary results from 177 mothers and infants that had completed the initial questionnaire by August 1st 2013, whose children had been born prior to April 1st 2013. A simple analysis of demographics from the results from the initial questionnaires of mothers that were recruited during the pilot phase of the LRBCS has already been performed and described elsewhere.⁽²⁰⁵⁾ Following the analysis of data from the pilot group, the research team felt it was necessary to further develop the questionnaire and some questions that investigated whether parents had visited their GP with concerns about their child's respiratory symptoms, or whether the child had been admitted to hospital with respiratory symptoms. The research team also felt it would be useful to obtain a record of maternal age, to ensure that the technology used in the LRBCS does not introduce bias. A full analysis of results of the initial questionnaire will be performed when all mothers who wish to participate in the study have completed the questionnaire.

5.1.1 Aims

The primary objective of this preliminary analysis of responses to the initial LRBCS questionnaire was to create a profile of the children, mothers and households involved with the LRBCS up until 1st August 2013. The analysis also aimed to identify whether the mothers that were fully consenting and completing the first questionnaire were a representative sample of mothers living in Liverpool. Furthermore, it aimed to identify whether there were any differences in the LRSQ scores from different population groups. This analysis also aimed to further assess the internal validity the eight domains of the LRSQ.

5.2 Methods

5.2.1 Distribution of Questionnaires

Email

Questionnaires were distributed to mothers wished to participate online using an invitation email that contained the Uniform Resource Locator (URL) for the initial questionnaire. Invitations were sent on a rolling, daily basis, when the child had reached age four months. The invitation email contained a mothers Unique Identification (ID) code that would be entered on the first screen of the questionnaires (see Appendix 11 for instructions how to access an example questionnaire). This semi-anonymised ID consists of the first four letters

of a mother's surname, the initial of the mother's first name, and the child's date of birth, followed by a number one for a singleton, or one or two for twins etc. This ID will be the sole method of identifying mothers in follow-up questionnaires, and is also necessary for the future longitudinal linkage of cohort data.

Postal Questionnaires

Postal questionnaires were distributed in batches on a weekly basis. The content and themes of the postal questionnaire was identical to that of the online version, however some adjustment were made to the layout to ensure it was suitable in an A4 page format (see Appendix 12 for the complete postal questionnaire). The postal questionnaire was sent alongside a covering letter that had similar content the invitation email, as well as a consent form, information sheet, and a stamped and addressed return envelope. Recipient's addresses and postcodes were validated prior to sending, and were amended using the child's record on the MEDITECH© system at Alder Hey Children's Hospital if necessary. The back of the envelope contained a return address to ensure the research team could identify if any of these postal questionnaires could not be delivered.

Invitations and Reminders

Previous studies have demonstrated that communications reminding participants to complete questionnaires can significantly enhance response rates in both online and postal questionnaires.^(208, 209) The research team received ethical approval to distribute questionnaires by email or by post on a six monthly basis to mothers who had fully consented to participate in the study. Additionally, the research team obtained permission to send up to three subsequent email reminders to invite mothers to participate at weekly intervals. Furthermore, should the mother not respond to these invitations within four weeks, the research team was permitted to contact the mother by telephone to ascertain whether she still wished to participate in the study or not.

Batch Tracing

An encrypted list of all recruited infants (including expressions of interest) is sent to the IT Department at Alder Hey Children's Hospital on a weekly basis by the research team. Information analysts cross-reference the list against MEDITECH© records for children, in order to identify whether any participants have deceased. The list is subsequently returned to the research team to ensure that these patients are removed from the active study database, which in turn prevents parents from receiving questionnaires and/or reminders regarding a deceased child.

5.2.2 Data Collection and Storage

Data from online questionnaires was automatically collected in to a database securely hosted by Adobe®FormsCentral. Data from returned postal questionnaires was manually added to this database. Data could be exported periodically or as it was required, and an encrypted and password protected version could be stored on University of Liverpool servers.

5.2.3 Data Analysis

Demographics and Exposures

The LRBCS is still early in its data collection phase, thus only preliminary data is available for analysis in this thesis. Therefore, a general descriptive analysis was performed on this dataset using Statistical Package for the Social Sciences (SPSS) Version 20. Chi-Square was used to calculate whether demographics of respondents to the initial questionnaire were a represented sample of the population. Data relating to the demographic and exposure variables of participants was compared to local, regional or national figures, depending on the availability of data. Population demographics sources were the online sources of the Office for National Statistics (ONS), the Child and Maternal Health Intelligence Network (ChiMat) and the Health and Social Care Information Centre (HSCIC), all accessed between the 1st and 18th of August 2013.

Deprivations scores were calculated by inputting postcodes in to the Manchester Information and Association Services (MIMAS) data analysis software package, which converts postcodes into deprivation scores. Scores were subsequently assigned to quintiles; quintile one represents the most affluent 20% of the UK population, whereas quintile five represents the most deprived. These deprivation scores combine a range of economic, social and housing indicators to provide an up to date, comprehensive overview of deprivation in England.⁽²¹⁰⁾

Details about the mother's pregnancy and birth were as recalled by the mother. Cigarette smoke exposure during pregnancy (active and passive) were also self-reported. Gestation at birth was recorded in completed weeks of pregnancy. The questionnaire permitted parents to enter their child's birth weight in either metric (Kilograms) or imperial (Pounds and ounces). All birth weights were subsequently converted by a member of the research team in to grams (g). Ethnicity was recorded as the ethnic group or background from the UK Census 2011 to which mothers felt their child belonged.⁽²¹¹⁾

LRSQ Scores

The LRSQ contains eight domains that each contain between three and five items. Each item contains a 5-point Likert scale ranging from 0-4, where 0 corresponds to no symptoms in the last three months, and 4 corresponds to symptoms every day or night in this time period. LRSQ scores can be calculated out of a maximum of 132 (100 points for respiratory symptoms and 32 for quality of life). Overall scores were calculated during this preliminary analysis, and were cross tabulated with important exposures including prematurity, breast feeding and exposure to household tobacco smoke scores. Time constraints do not permit for multivariate analysis, or comprehensive analysis of scores in each of the LRSQ domains.

Questionnaire Validity

Cronbach's α coefficients were calculated to assess internal consistency of items within individual questionnaire domains, indicating the extent to which they measured the same construct.

5.3 Results

5.3.1 Response Rates

By the beginning of August 2013, the LRBCS research team had distributed the consent for and initial questionnaire to 705 mothers. Of these, 485 questionnaires had been sent by email and 220 had been sent by post. 39 of the 220 postal questionnaires were sent to mothers who had indicated that they would prefer to be contacted by email, but whose emails had subsequently “bounced”, and thus were invalid and failed to be delivered. The 39 mothers with invalid email addresses had previously been identified by Mailchimp®.

177 mothers had returned the questionnaires about their child by the cut-off point of the 1st of August, thus the response rate for the initial questionnaire is approximately 25%. 33% (n=160) of the 485 mothers who were sent a study invitation by email completed the online questionnaire via Adobe®FormsCentral, and 8% (n=17) of the 220 mothers returned postal questionnaires.

5.3.2 Profile of the LRBCS Mothers, Families and Households

Deprivation

The Indices of Multiple Deprivation (IMD) 2010 scores for socioeconomic deprivation were derived from the household postcodes that mothers provided on expression of interest postcards and on the contact details section of the initial questionnaire. The deprivation quintiles of all mothers who had consented and completed the initial questionnaire were then calculated using these scores, and the number and percentages of mothers belonging to each quintile was calculated by had expressed interest in the study, and with all eligible births at LWH during the same time period (Figure 5.1). Previous analysis of preliminary results from the pilot group of participants demonstrated that mothers that expressed interest in the study were a representative sample of all women giving birth at LWH in the context of socioeconomic deprivation.

This analysis demonstrated that small differences existed in the deprivation scores of mothers from who had fully consented and completed the first questionnaire compared to all mothers giving birth at LWH during the same period, and those who expressed interest in the study ($X^2=11.025$, $p=0.087$).⁽²⁰⁵⁾ Therefore, mothers from the most deprived quintile may be underrepresented in the sample, whereas mothers from the most affluent areas may be over represented. Analysis was also performed upon the deprivation quintiles of mothers selecting to receive questionnaires by email or post, compared to all births at LWH. Mothers from the least deprived postcodes showed a preference towards web based surveys, whereas mothers from the most deprived areas showed a slight preference towards postal questionnaires ($X^2=7.417$, $p=0.059$)(Figure 5.2).

Figure 5.1 Proportion of mothers belonging to each IMD Quintile

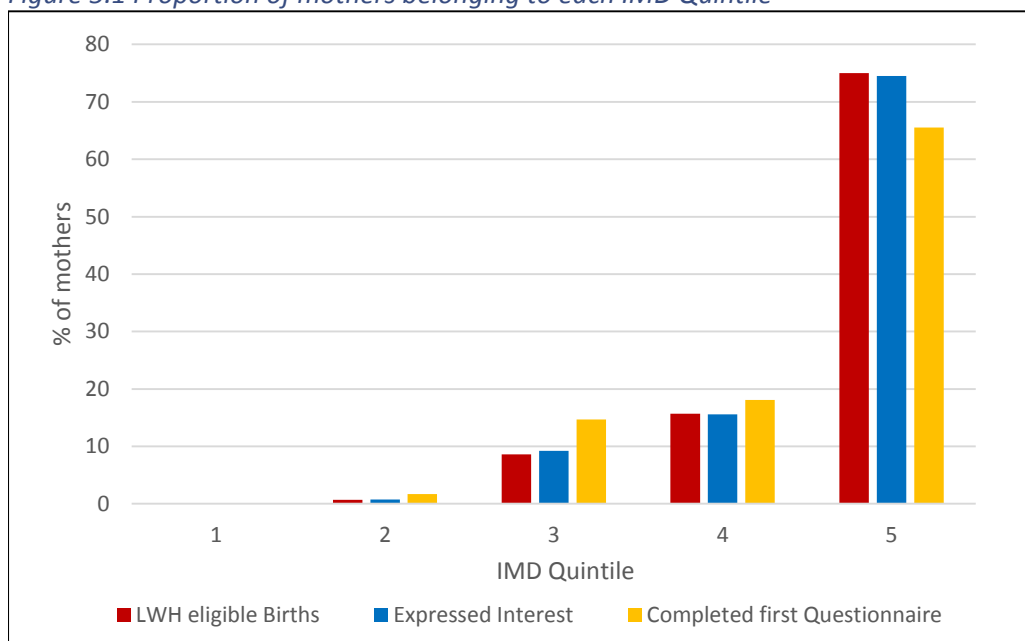
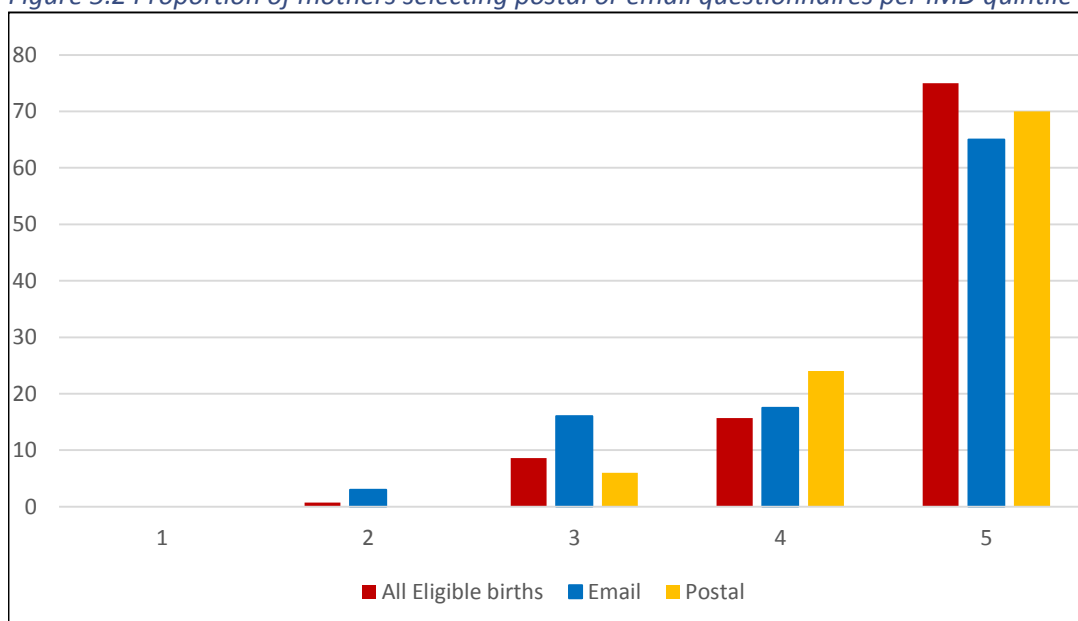


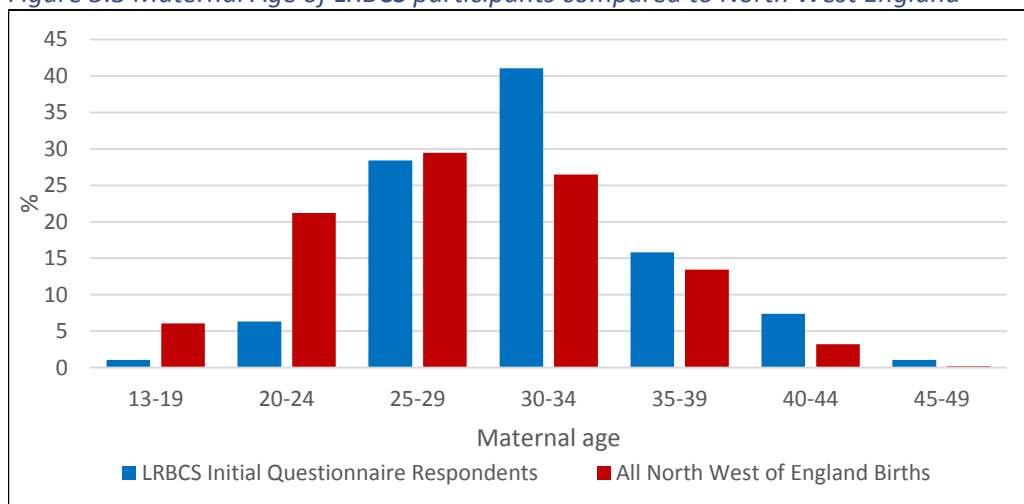
Figure 5.2 Proportion of mothers selecting postal or email questionnaires per IMD quintile



Maternal Age

Maternal age was one of the questions that were added to the questionnaire following the analysis of questionnaires returned from the pilot group. Therefore, data about maternal age is therefore available for 53% (n=94) of respondents. The mean age of mothers completing the questionnaire was 31 years and 3 months of age. The youngest and oldest mothers to complete the questionnaire were 19 and 45 years, respectively. Therefore, the range of maternal age was 26 years. This data was compared to maternal age figures for the North West of England Strategic Health Area (NWSHA), from the HSCIC's Hospital Episode Statistics (Figure 5.3).⁽²¹²⁾ This demonstrated that mothers that responded to the initial LRBCS questionnaire when their child was four months old were significantly older than all mothers giving birth in the North West of England ($\chi^2=27.075$, $p<0.001$).

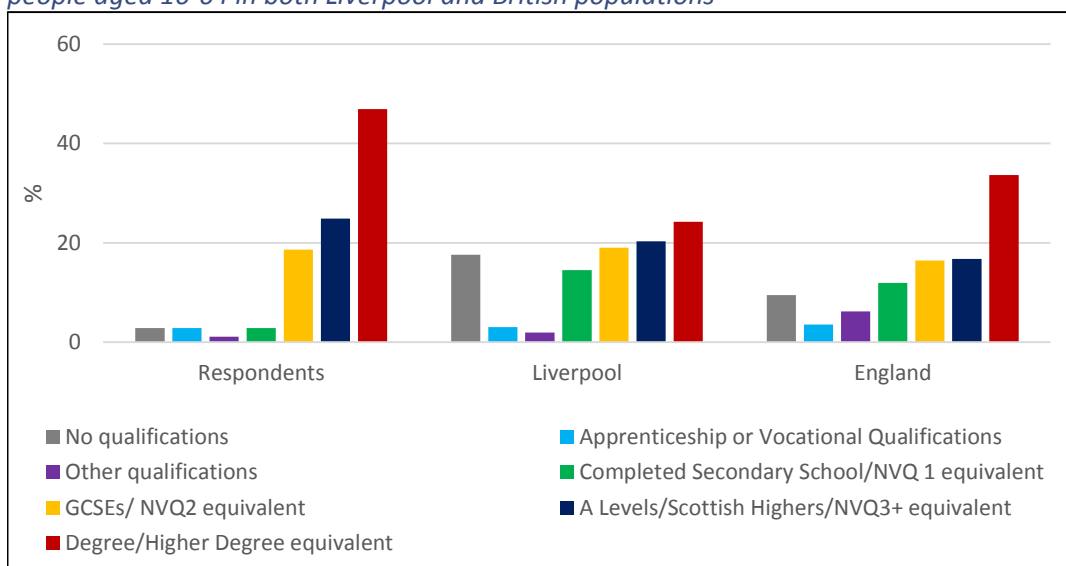
Figure 5.3 Maternal Age of LRBCS participants compared to North West England



Education

All 177 mothers responded to the question relating to the highest level of educational achievement they had attained. 6% of mothers (n=10) reported that they had no qualifications, and 47% (n=83) of respondents reported having achieved either an undergraduate or postgraduate degree. This data was compared to data relating to the levels of educational achievements for Liverpool and UK populations aged 16-64 years from the Office of National Statistics NOMIS database (Figure 5.4).⁽²¹³⁾ This comparison demonstrated that mothers who responded to the initial LRBCS questionnaire had been educated to a higher level than the general Liverpool population ($\chi^2=78.828$, $p<0.001$). Mothers that had higher level qualifications were more likely to complete the questionnaire, whereas mothers with no or level 1 qualifications are considerably underrepresented in the sample.

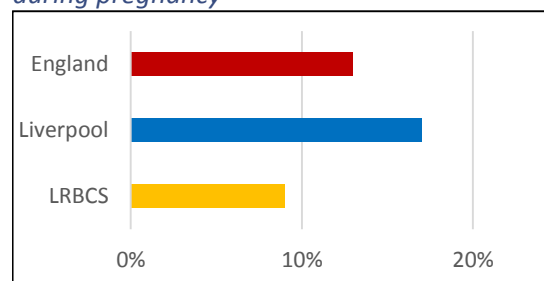
Figure 5.4 Highest Educational Qualification attained of LRBCS respondents compared to people aged 16-64 in both Liverpool and British populations



Cigarette Smoking

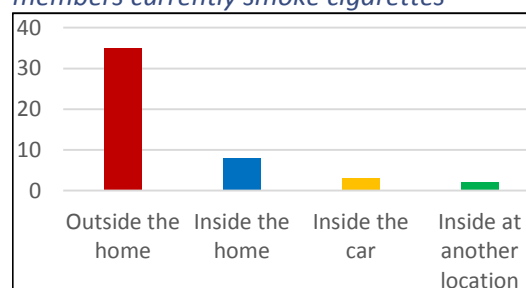
There were three questions that related to cigarette smoking within the household. One question explored active (maternal) smoking during pregnancy, and one related to passive exposure to cigarette exposure during pregnancy. The third related to any household member (including the mother) that currently smoked cigarettes. 9% (n=16) of mothers who completed the questionnaire reported that they had smoked whilst pregnant (Figure 5.5).

Figure 5.5 Prevalence of cigarette smoking during pregnancy



This number was significantly lower than the reported prevalence of smoking during pregnancy in the Liverpool population ($X^2=7.773$, $p<0.005$), and was also lower than the national average for England ($X^2=2.767$, $p=0.096$).⁽²¹⁴⁾ Furthermore, 19% (n=33) mothers reported that another household

Figure 5.6 Locations where household members currently smoke cigarettes



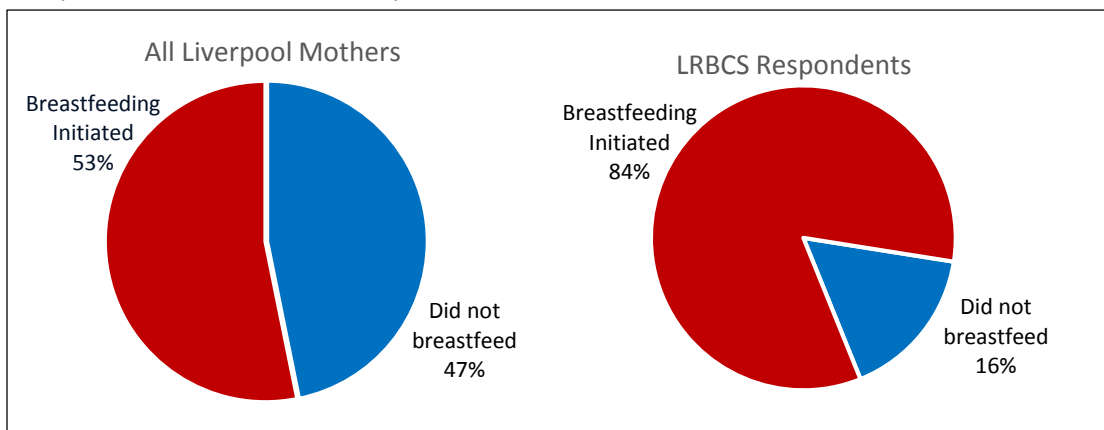
member smoked during her pregnancy, and thus may have been passively exposed to cigarette smoke. 20% (n=35) of mothers report that a household member currently smokes

cigarettes. Of these, 33 reported they smoked outside the home, eight reported smoking inside and three reported smoking cigarettes in the car (Figure 5.6).

Breast Feeding

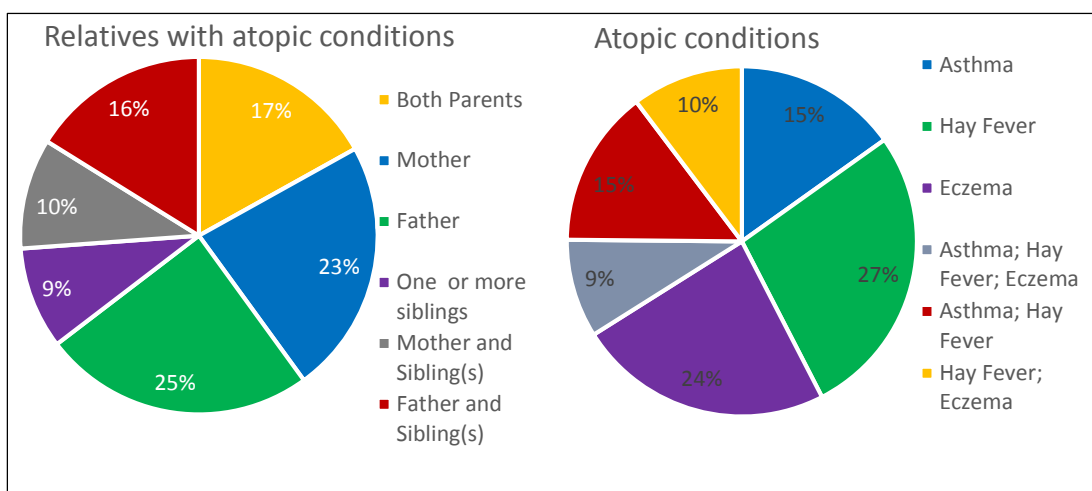
The questionnaire asked mother to identify whether her child had ever been breastfed, either exclusively or supplemented with infant milk formula. If the mother indicated that she had breastfed her child, she was asked to specify whether this had been for up to one month, 1-3 months or was still breastfeeding. 84% (n=148) of mothers reported that their child had been breastfed. This is significantly higher than the number of mothers living in the Liverpool PCT area who initiated breastfeeding in 2012 ($X^2=59.484$, $p<0.001$) (Figure 5.7).⁽²¹⁵⁾ 44 of these mothers had breastfed for 1 month or less. Therefore, 70% (n=104) of all mothers that had initiated breastfeeding continued to do beyond 1 month of age, and 47% (n=70) of mothers that initiated breastfeeding continued to breastfeed their infant at the time of the initial questionnaire.

Figure 5.7 Proportion of mothers who fully enrolled in the LRBCS that initiated breast feeding compared to all mothers in Liverpool



Atopic Disease

The questionnaire explores family history of atopy by asking mothers to identify whether they or any first degree relatives (parents or siblings) have been diagnosed with Asthma, Hay Fever or Eczema by a doctor. 75% (n=130) of respondents reported that there was a family history of atopy one or more siblings (n=30), the child's mother (n=66), and or the child's father (n=65)(Figure 5.8).

Figure 5.8 Atopic conditions in first degree relatives of LRBCS children

5.3.3 Profile of Infants Fully Enrolled in the LRBCS

Sex

The cohort of children who were fully enrolled in the study consisted of 51% (n=90) females and 49% (n=87) males. There is no significant difference in the male to female sex ratio of children enrolled in the LRBCS compared to the sex ratio of the Liverpool population ($X^2=0.005$, $p=0.944$).⁽²¹³⁾

Multiple Births

Two sets of twins have been enrolled in the LRBCS. Therefore, twins account for approximately 1% of responses. Multiple births accounted for approximately 1.6% (n=11,505) of all births in the UK in 2011. There is no difference in the representation of twins in cohort compared to all births in England ($X^2=0.216$ $p=0.641$).⁽²¹⁶⁾

Ethnicity

Of the 177 mothers, 99% (n=175) stated the child's ethnicity, and 1% (n=2) expressed that they would prefer not to state their child's ethnicity. Of all mothers that responded, 91% (n=159) described their infants as of White British background, and a further 4% (n=7) of infants were described as any other White ethnic background. It is not yet possible to perform chi-squared analysis to ascertain whether there is any significant difference in the ethnicity of LRBCS infants in comparison to the Liverpool population as there have been no questionnaires returned for children of Asian or Asian British background. However, there is a trend emerging in which mothers of infants of White British ethnic background are overrepresented in the sample. Table 5.1 shows the number and percentage of infants

belonging to each ethnic group in the LRBCS infants compared to the whole Liverpool population.⁽²¹³⁾

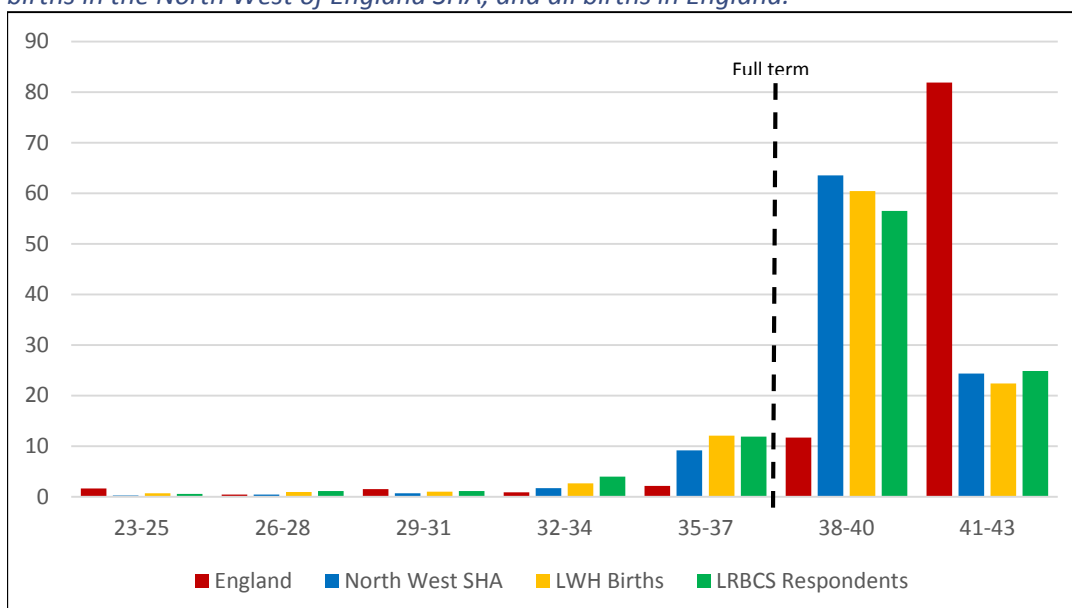
Table 5.1 Representation of ethnic groups within the cohort of fully enrolled children compared to the Liverpool population

Ethnic Group	Recruited Infants	Liverpool Population
<i>White British</i>	159 (91%)	402214 (85%)
<i>Other White</i>	7(4%)	12272 (3%)
<i>Mixed</i>	7(4%)	11756(3%)
<i>Asian or Asian British</i>	0(0%)	19403(4%)
<i>Black or Black British</i>	1 (1%)	12308(3%)
<i>Chinese or other ethnic group</i>	1(1%)	11414(2%)

Gestation at birth

Gestation at birth in completed weeks of pregnancy was recorded as recalled by the mother. Of the 177 infants that had been fully enrolled in the study, 19% (n=33) were born at 38 or more weeks gestation, which is classified as full term. 18% of all infants born at LWH in 2011-12 were born at full term. There is no statistically significant difference between these two figures ($\chi^2=0.248$, $p=0.618$), and thus the gestation at birth of infants enrolled in the LRBCS is representative of all births of the hospital. Furthermore, these figures also reflect statistics for gestation across the North West of England region.⁽²¹²⁾ However, this analysis demonstrated that significantly more children in enrolled in the LRBCS are born prematurely compared to all births nationally ($\chi^2=46.061$, $p<0.001$).⁽²¹²⁾ Figure 5.9 demonstrates the gestation at birth in weeks of all infants enrolled in the LRBCS, compared to all infants born at LWH, in the North West of England, and England as a whole.

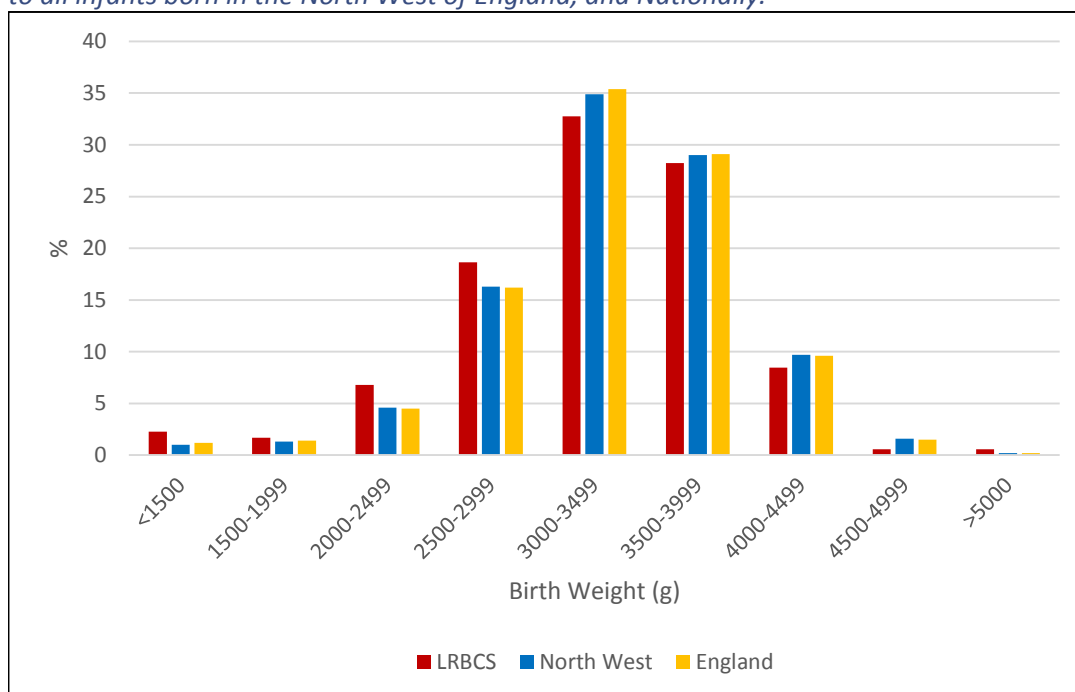
Figure 5.9 Gestation of infants enrolled in the LRBCS, compared to all births at LWH, all births in the North West of England SHA, and all births in England.



Birth Weight

The mean birth weight for infants enrolled in the LRBCS is 3258g. The lowest birth weight recorded was 510g, and the highest was 5500g, thus the range was 4990g. 11% (n=19) of infants had low birth weights (LBW), and 4% (n=7) had a very low birth weight, which are classified as a birth weight of less than 2500g and 1500g, respectively regardless of gestational age. Children enrolled in the LRBCS had slightly lower birth weights than children in the North West region, but this difference is not significant ($X^2=7.923$, $p=0.448$). The birth weights of children enrolled in the study were not significantly lower than those of all English children ($X^2=7.967$, $p=0.446$) (Figure 5.10).

Figure 5.10 Distribution (%) of Birth Weight of infants fully enrolled in the LRBCS compared to all infants born in the North West of England, and Nationally.



Co-Morbidities

The questionnaire asked mother whether their child had been diagnosed with any chronic health conditions or diseases. 9% (n=16) of mothers indicated that their child had a chronic disease. Five children had been diagnosed with respiratory disease; two with cystic fibrosis, two with bronchopulmonary dysplasia, and one with a congenital deformity of the respiratory tract. A further three children had neurological conditions, three had gastrointestinal conditions, and two children had congenital heart defects.

Contact with healthcare services due to respiratory disease

Questions relating to the incidence and frequency of GP and Hospital visits or admission for respiratory conditions were added following analysis of the pilot results. This data is

therefore available for 103 participants. 16% (n=16) of mothers had taken their infant to the GP for respiratory related concerns. Of these, 31% (n=5) had visited the GP more than once because of these concerns. 4% of infants had been admitted to hospital due to a respiratory condition in the first three months of life.

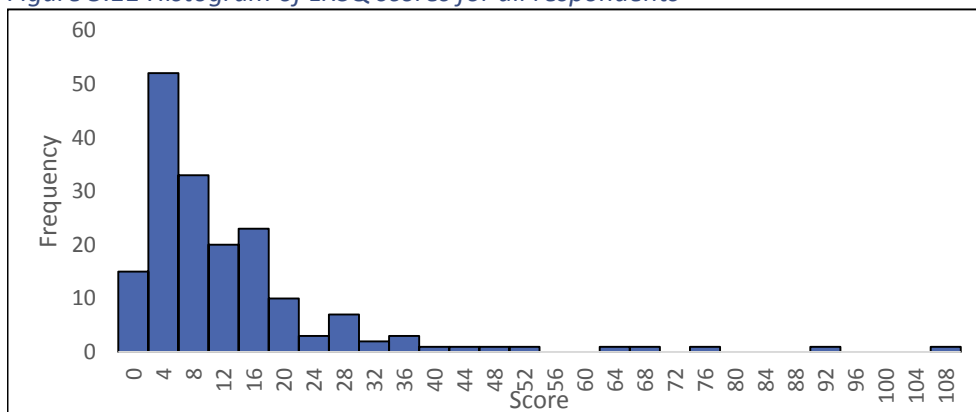
5.3.4 The Liverpool Respiratory Symptom Questionnaire

LRSQ scores out of a maximum of 132 were calculated for each participant. The lowest score was zero, and the highest score was 108. The mean score was 11, the median was 6 and the mode was 0. The standard deviation for all LRSQ scores was 15.4.

LRSQ Scores in relation to specific exposures

Higher mean LRSQ scores were observed in children that lived in a household where at least one person smoked cigarettes, irrespective of whether this person or persons smoke inside or outside the home. The median scores of smoking and non-smoking households were 5, and 2, respectively. Questionnaire scores were not normally distributed (Figure 5.11), therefore a Mann-Whitney U test was conducted to evaluate the differences in responses to the questionnaire. Living in a household with smokers had a significant effect upon the LRSQ scores of infants (The mean ranks of smoking households versus non-smoking household were 113 and 83, respectively; $U=1618$, $Z=-3.23$, $p<0.001$, $r=0.24$).

Figure 5.11 Histogram of LRSQ scores for all respondents



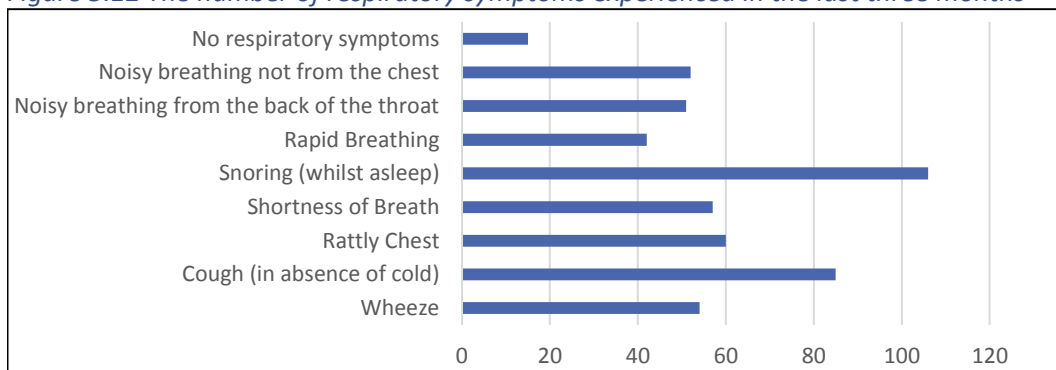
Children that were ever breastfed, regardless of duration, had lower mean LRSQ scores than children that had not been breastfed (mean scores 12 and 16, respectively). However, Mann-Whitney U testing demonstrated that the effect size of breastfeeding upon LRSQ was small and probably not significant ($U=2555$, $Z=-0.811$, $p=0.417$, $r=0.06$). There was only a small non-significant difference in the mean scores of premature infants (born at less than 38 weeks gestation) and infants born at full term, which were 11 and 12 respectively ($U=2171$, $Z=-0.733$, $p=0.439$, $r=0.05$). There were also small non-significant differences between the mean scores of children from the most deprived quintile of the

Liverpool population, and children from the other four quintiles, which were 13 and 9, respectively ($U=3112$, $Z=-1.232$, $p=0.218$, $r=0.09$).

The prevalence of Respiratory Symptoms in infants aged 1-4 months living in Liverpool

Snoring was the most frequently occurring symptom, with 106 of 177 respondents indicating that their child had snored whilst asleep in the last three months. Mothers of 8% ($n=15$) of the 177 children fully enrolled in the study reported that their child had not experienced any respiratory symptoms in the last 3 months. 31% ($n=54$) of mothers reported in at least one of the five symptom domains that their child had wheezed in the last three months. The prevalence of cough across all these domains was 58% ($n=104$). 11% ($n=19$) children only suffered from cough with a cold, however 48% ($n=85$) mothers reported that their child had a cough in the absence of a cold. 34% ($n=60$) of infants had experienced the symptom of a rattly chest, and 33% ($n=57$) of children had experienced shortness of breath. Other symptoms experienced by infants included rapid breathing ($n=42$), noisy breathing from the back of the throat ($n=51$), and noisy breathing that does not come from the chest ($n=52$) (Figure 5.12). 67% ($n=119$) children had experienced a cold in the last three months, and 24% of children had suffered with multiple colds during this time period.

Figure 5.12 The number of respiratory symptoms experienced in the last three months

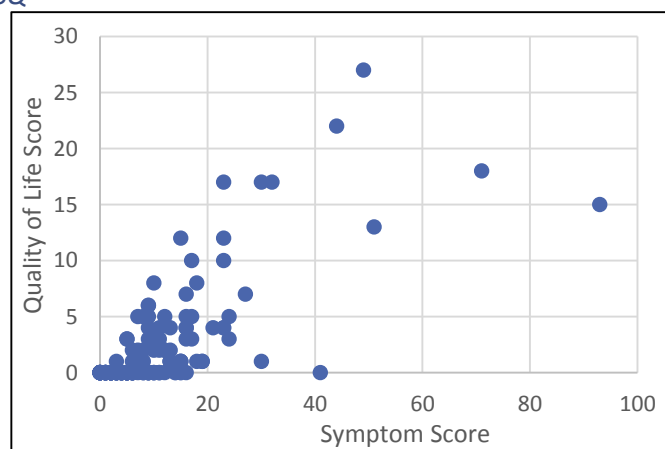


Higher scores in symptom domains appeared to be associated with higher scores in the quality of life domains, however there are a number of outliers (Figure 5.13). A significant limitation of the comparison of symptom score domains (domains 1-6 of the LRSQ), against scores in the quality of life domains (domains 7 and 8), was that this analysis has not previously been undertaken or validated in other studies that used the LRSQ.^(1,7) Therefore, although there seems to be a correlation between the severity of symptoms and the severity of the impact upon quality of life, which is associated with high scores in the respective domains, the validity and significance of these differences is yet to be

determined. Further analyses may be undertaken at a future date using the full sample to determine these factors.

Individual scores of each of the eight domains of the LRSQ were also appraised during this analysis. This was in order to assess whether specific exposures, such as household tobacco smoke had any effect upon the scores of individual domains. However, it was discovered that the sample is currently too small, and thus there is currently insufficient data to be able to detect significant differences in domain scores between groups of exposed children and groups of protected or not exposed infants.

Figure 5.13 The relationship between symptom domain scores and quality of life domain scores in the LRSQ



The effect of respiratory symptoms upon the child's quality of life

27% (n=47) of mothers reported that respiratory symptoms had some effect upon the quality of life of their child during the last three months. 20% (n=36) of mothers reported that their child had been awoken from sleep by their respiratory symptoms, and 18% (n=32) children had experienced difficulty feeding in the last three months as a consequence of their respiratory symptoms. 7% (n=13) of mothers noted that their child had been unusually tired as a result of these symptoms.

The effect of respiratory symptoms upon the mother and family's quality of life

29% (n=51) of mothers reported that they had been concerned about their child's respiratory symptoms during the last three months. 23% (n=40) of mothers reported that their sleep had been disturbed by their infants respiratory symptoms. 10% (n=18) of mothers reported that their child's respiratory symptoms had limited their activity, and 8% (n=15) of mothers stated that symptoms had resulted in adjustments being made to their daily life.

5.3.5 Validation of the Liverpool Respiratory Symptoms Questionnaire

The internal consistency of the LRSQ portion of the questionnaire was assessed using Cronbach's alpha coefficients. The domain exploring the effect of a child's symptoms upon the family demonstrated excellent internal consistency ($\alpha > 0.9$). Furthermore, the domain exploring the child's quality of life demonstrated good internal consistency, as did the domain that explored respiratory symptoms with colds ($\alpha > 0.8$). Four domains had acceptable internal consistency ($\alpha > 0.7$). However, the domain that explores "other respiratory symptoms" had questionable internal consistency, with a Cronbach's alpha coefficient of 0.688. Therefore, seven out of the eight domains of the LRSQ had acceptable or better internal consistency, demonstrating that the questionnaire overall has acceptable-to-good internal consistency (Table 5.2).^(217, 218)

Table 5.2 Internal Validity of the Liverpool Respiratory Symptom Questionnaire

Domain	Symptoms in last 3 months	Cronbach's Alpha	Internal Consistency
1	Daytime symptoms	0.701	Acceptable
2	Night time symptoms	0.704	Acceptable
3	With Colds	0.828	Good
4	Intermittent symptoms	0.723	Acceptable
5	During Activity	0.791	Acceptable
6	Other symptoms	0.688	Questionable
7	Effect on Child	0.838	Good
8	Effect on family	0.901	Excellent

5.4 Discussion

5.4.1 Response Rates

Response rates to both online and offline questionnaires can vary significantly between studies, depending on the population, the properties of the questionnaire and the purpose of the study.^(162, 163, 209) A general decline has been reported in the response rates to questionnaires used in medical research and epidemiological studies over the past two decades for all study designs.^(219, 220) The participation rate for the LRBCS was 25% of mothers who had expressed interest in the study around the time of the birth of their child. The return rate for the postal questionnaire, at 7%, was disappointing. The research student spent a considerable amount of time each week upon administering postal questionnaires.⁽²²¹⁾ The research team were satisfied with the return rate of 33% of the email questionnaire in comparison to rates from other cohort studies.^(175, 178, 219, 222)

The analysis of responses demonstrated that mothers that were living in deprived postcode areas were more likely to request postal questionnaires, and mothers from the most affluent areas of the city were showed preference towards a web-based questionnaire. Therefore, despite the limitations and low response rates of postal

questionnaires in this study, it is essential that the postal option remains for mothers to minimise bias, and ensure that children from the most deprived areas are not underrepresented in the cohort.

5.4.2 LRBCS Mothers, Households and Families

Liverpool is one of the most socioeconomically deprived cities in the country, and around 75% of the city's population are amongst the most deprived in England. The Toxteth area of the city is the most deprived area in the country.^(210, 223) Furthermore, social deprivation is an important risk factor for respiratory disease in Liverpool's paediatric population.^(27, 38) It is therefore essential that the cohort of children that are enrolled in the LRBCS are a representative sample of children in Liverpool in the context of socioeconomic deprivation. There were slightly less expressions of interest from mothers of children from the most deprived quintile compared to all births in the hospital, and furthermore, slightly less mothers consented and completed the first questionnaire from the most deprived quintile. This difference is, as yet, non-significant. However, the p-value is trending towards significance, and the research team expects this difference to become more prominent as the sample size increases.

Mothers living in Liverpool are ranked in the lowest quartile nationally for initiation of breastfeeding rates.⁽²¹⁵⁾ Despite this, over 80% of mothers participating in the LRBCS recorded that their child had been breastfed, which is significantly higher than the average national level. It appears that children enrolled in the study are therefore much likelier to have been breastfed. This may reflect a recent targeted health promotion initiatives and peer support and information services available to mothers delivering at LWH. However, it must be considered that there may be some reporting bias on behalf of mothers, who, due to various health promotion initiatives, feel pressurised to report that their child had been breastfed. This self-reporting bias in the context of breastfeeding has been reported elsewhere.⁽²²⁴⁾

The spread of gestation at birth of infants enrolled in the LRBCS reflected those of all infants born at the Hospital, and were also representative of all infants born in the North West of England. However, significantly more children in the region are born prematurely compared to England. The Liverpool population has an increased prevalence of a number of socioeconomic and sociodemographic that have been associated with premature birth, including higher levels of teenage pregnancies, social deprivation and cigarette smoking during pregnancy.^(138, 225-227)

Children of mothers who smoke are more likely to develop asthma, and maternal smoking has been associated with receiving a shorter education.⁽²²⁸⁾ The level of maternal smoking reported in the LRBCS was lower than the regional average, thus self-reporting bias may be present. However, mothers who have opted to participate in the LRBCS are generally more educated than all women delivering at LWH which may explain why the number of mothers who reported smoking during pregnancy in the LRBCS were much lower than official governing bodies.⁽²¹⁴⁾

The profile of mothers participating in the LRBCS differed in a number of demographics in comparison with all women giving birth in the region. If these differences are demonstrated to have significant effects upon LRSQ scores, the research team will need to correct results for future questionnaires to adjust for these differences.

5.4.3 LRBCS Infants

The sample of infants participating in the LRBCS were relatively representative of the Liverpool population in terms of sex, gestation and birth weight. Similarly to other birth cohorts, children of White British ethnic origin were overrepresented in the cohort compared to the Liverpool population.⁽⁶⁴⁾ This may be attributed to the exclusion criteria of the study, whereby mothers that could not speak English were not invited to register their interest in study. The decision for this criterion was based upon the limited availability of funding of the study, meaning that it would not be feasible to translate questionnaires to different languages, which has been possible in other studies.⁽⁶⁶⁾ Automated translating facilities such as GoogleTranslate would not be appropriate to translate the LRBCS information sheets, consents forms and questionnaires as each translation would require validation by a qualified interpreter to ensure the meaning of questionnaire items was not lost.

5.4.4 The Liverpool Respiratory Symptom Questionnaire

It is promising that significant results have been obtained from the LRSQ, despite this analysis being performed on just a fraction of the anticipated sample for the first LRBCS questionnaire. The most significant results were that the LRSQ scores of children that were exposed to household tobacco smoke were significantly higher than children who did not share a household with a smoker. Differences were also detected in other population groups that are considered at risk of respiratory disease, which included children from deprived areas, children who were never breastfed and children who were born prematurely.^(39, 88, 229, 230) The sample size of the LRBCS is still small, thus the size of effect of these factors upon LRSQ may become more evident as the number of children enrolled in

the study increases. Future analyses should investigate the roles of protective and exacerbating factors for respiratory symptoms in children, such as breastfeeding and cigarette smoking upon questionnaire scores.

The questionnaire also revealed that there is a relatively high prevalence of respiratory symptoms during the first three months of life, particularly snoring and cough. Cough may be attributed to a number of respiratory and non-respiratory conditions, thus the significance of this high prevalence in the context of the LRSQ is not yet clear. This demonstrates that these “symptoms”, particularly snoring, are in fact normal elements of respiratory function. It was only possible to assess the presence of these symptoms across all domains in this analysis. Future analyses should assess the significance of the presence and severity of these symptoms in each domain to gain further insight in to the dimensions of respiratory symptoms in this population.

5.4.5 Validity of the LRSQ

Assessment of the internal consistency of the LRSQ demonstrated that the LRSQ is an acceptable tool for assessing respiratory symptoms in a population based sample of infants aged four months. Cronbach’s alpha coefficients for internal consistency is acceptable or better in 7 out of 8 domains (Table 5.3). However, the coefficients were considerably lower for LRBCS participants compared to the initial analysis by Powell et al. This may be attributed to the coefficients for the LRBCS being calculated for eight domains, whereas Powell et al grouped the four domain that explore daytime symptoms together. A larger number of items in a questionnaire domain has been demonstrated to raise the Cronbach’s alpha scores. The internal validity of the night time symptoms increased to 0.784 when the question relating to snoring was removed from analysis. Improvements in the validity of this domain with the removal of the snoring question were described in both other studies that validated the questionnaire.^(1, 7) If this item persists to lower the validity of this domain when all responses to the initial questionnaire have been received, the research team will consider removing this question for analysis in order to enhance the validity of the LRSQ.

Table 5.3 Cronbach's Alpha scores for LRSQ domains in the LRBCS compared to previous studies that have used the questionnaire

Domain		LRBCS	Trinick et al ⁸ (preschool group)	Powell et al ¹
1	Daytime symptoms	0.70	0.76	0.95*
2	Night time symptoms	0.70	0.64	0.80
3	With Colds	0.83	0.66	0.95*
4	Intermittent symptoms	0.72	0.81	0.95*
5	During Activity	0.79	0.79	0.95*
6	Other symptoms	0.69	0.80	0.95*
7	Effect on Child	0.84	0.89	0.87
8	Effect on family	0.90	0.79	0.91

*Domains 1 and 3-6 (Day time symptoms) were grouped together for Cronbach's alpha analysis by Powell et al

5.4.6 Strengths

Longitudinal population-based birth cohort studies have a number of strengths and limitations, which are discussed in chapter six of this thesis. This preliminary analysis of initial questionnaire results are useful as the primary outcome measure of the LRBCS, had been previously validated to assess parent-reported respiratory symptoms in preschool children. This analysis has demonstrated that differences exist in the symptom scores of children that had risk factors for respiratory conditions in childhood. Significant differences exist in the LRSQ scores of children exposed to cigarette smoke compared to infants with non-smoking households members. This will help researchers focus further analysis of results from this questionnaire and future questionnaires.

A further strength of this analysis is that it has further validated the LRSQ in a cohort of healthy infants aged four months. The study aimed to recruit a large number of mother and infants from LWH, who were a representative sample of the Liverpool population. The analysis of results has demonstrated that the sample of mothers and infants enrolled in the study are not perfectly representative of the Liverpool population, however statistical analysis has demonstrated that the differences between the demographics of the two groups are currently relatively small.

The quality of data received by the research team, and there were no incomplete questionnaires. This may be attributed to some function of the online questionnaire, which does not allow a respondents to proceed to the next section or submit their responses with incomplete or invalid responses.

5.4.7 Limitations

Despite these strengths, this analysis has a number of limitations that must be considered. It was not yet possible to assess the sensitivity of the LRSQ in detecting changes in respiratory symptoms longitudinally. Furthermore, this analysis has been performed prior to the completion of recruitment to the study, thus the sample is incomplete and children that are currently enrolled may not be representative of the final sample. Sampling bias may be present in these results.

The seasonality of respiratory symptoms is of particular concern in this analysis, as it has been performed on infants born between the months January and April. The incidence of respiratory symptoms in this group may therefore be exaggerated, as respiratory infections such as bronchiolitis during winter months are likely to cause an increase the prevalence of symptoms during winter months. Additionally, non-communicable mechanisms for respiratory symptoms, such as the exacerbation of asthmatic symptoms by cold air, may also be responsible for increased respiratory symptoms such as cough and wheeze during the winter months.⁽²³¹⁾ By recruiting infants for a whole year, and by measuring symptoms at specific ages, such as ages 4 and 10 months as opposed to cross-sectional surveys of all participants, it is hoped that the potential bias of seasonality will be reduced. Furthermore, the LRSQ contain domains that specifically refer to symptoms associated with respiratory tract infections, as well as domains that explore symptoms when the child does not have such infections, it may be possible for researchers to distinguish between infective and allergic mechanisms for respiratory symptoms within this defined population of preschool children.

It must also be considered that the LRBCS questionnaire itself may be biased. Recall bias may have been present as parents were asked to recall respiratory symptoms from the preceding three months. However, previous studies that used the questionnaire have reported that the tool has an acceptable short term reliability.^(1, 7) Self-reporting bias in questions relating to negative health behaviours such as cigarette smoking during pregnancy has been reported elsewhere, and may explain the lower than expected prevalence of cigarette smoking amongst mothers.

5.5 Conclusions

An analysis of preliminary results from the first LRBCS has demonstrated that the demographics of mothers enrolling their child in the study differ, to varying degrees, from those of all mothers living in Liverpool. LRBCS mothers are likelier to be domiciled in more affluent areas, to be older, of white British ethnicity, and to have been educated to a higher level. LRBCS mothers were also less likely to smoke than the general Liverpool population,

and were more likely to initiate breastfeeding, and to continue breastfeeding beyond eight weeks than their regional and national counterparts.

Significantly higher LRSQ scores were associated with the presence of a household members who smoked, regardless of the location where this person smokes. A slightly lower mean LRSQ scores were observed in children who had ever been breastfed, and slightly higher scores were observed in children from socioeconomically deprived areas and those who were born prematurely.

Chapter 6

Questionnaire Development, Recruitment and Preliminary Results from the Liverpool Respiratory Birth Cohort Study

6.1 Discussion

The Liverpool Respiratory Birth Cohort Study has made significant progress during the last year. The research team have successfully developed and finalised the questionnaire content and design, created recruitment material, and have conducted feasibility and pilot studies using mothers from the target population. The study has now entered its data collection phase, and has already obtained significant results. To date, the research team have received 1685 expressions of interest in the study from mothers, and 220 of these mothers have fully enrolled their child in the study and completed the initial questionnaire. The LRBCS research team and LWH staff have not received any complaints, and a large proportion of new mothers that are approached by the research team express interest in the study.

The study has a number of unique features. It is the first study to longitudinally assess the respiratory symptoms and quality of life of preschool children using the LRSQ. The study is the first birth cohort study to assess the respiratory symptoms of preschool children living in Liverpool, and furthermore the LRBCS is also the first online birth cohort study to be conducted in the UK. Longitudinal study designs have notorious difficulties with loss to follow up, however this study uses the latest technology to maximise engagement with parents, which is hoped will maximise retention.⁽²³²⁾ In 2012, 95% of UK households with children had a fixed internet connection, and 67% of adults used a computer on a daily basis.⁽²³³⁾ Therefore, a large proportion of people living in the UK have access to technology.

Furthermore, 100% of mothers who participated in one of the LRBCS feasibility studies indicated that they had access to the internet, and would be happy to complete an online questionnaire about the respiratory health of their child. The online LRBCS questionnaire is accessible by means of personal computer, tablet or smartphone, which further increases its scope. The development of a smartphone application may further increase participation in the study.⁽²³⁴⁾ The LRBCS has already demonstrated that it is feasible to conduct a population based cohort study using online questionnaires.

Conducting the study online has allowed researchers to keep study cost to a minimum, with invitation emails and reminders being distributed automatically through

MailChimp® email software. This also helps reduce the administrative burden of the study. Financial difficulties have previously been a burden to researchers and limited the power and reach of birth cohort studies, thus the prospect of a conducting a study with five-year follow up at a cost of less than £2 per participant is attractive.^(65, 177) The higher response rate to email as opposed to postal questionnaires that has been observed so far further supports the decision of the research team to conduct the study primarily online.

A number of elements of the online questionnaires, including the appearance, layout and even the software were selected and developed with input from mothers belonging to the LRBCS demographics. The research team hope this will enhance response rates to the questionnaire. Attempts to further engage with mothers will be made throughout the study, by providing regular study updates and sending birthday greetings.

Similar to other birth cohort studies, the researchers found that adopting a personal approach to recruitment was the best approach.^(64-66, 204) Just one mother registered her interest in the study by using the QR code, one deposited a postcard in the post box, and five infants were recruited by the neonatal unit staff. In contrast, the research students personally recruited 1678 mothers at LWH to the study between January and July 2013. This figure represents approximately 58% of eligible mothers who delivered at the hospital during this time period.

Participation rates for the initial questionnaire were 25%, which is satisfactory when compared to other cohort studies.⁽⁷⁶⁾ Mothers that opted to fully enrol in the study were older and more educated than the general Liverpool population. This self-selection bias has been observed in another birth cohort study that used online questionnaires.⁽¹⁷⁸⁾ Mothers were more likely to initiate breastfeeding, and were less likely to smoke cigarettes during pregnancy compared to other mothers in Liverpool. Infants enrolled in the study were generally representative of the Liverpool population, however the gestation at birth of children in the region was significantly lower than the national English average. This may be attributed to a number of factors, including socioeconomic deprivation.⁽³⁴⁾ Despite the study being early in its data collection phase, there have been some significant preliminary results. Higher LRSQ scores corresponded to a greater prevalence and severity of respiratory symptoms in the last three months. Slightly increased mean symptom scores were observed in children from socioeconomically deprived backgrounds, as well as infants who were born prematurely and those who were not breastfed. A significantly increased score was observed in children who were exposed to household tobacco smoke, which has previously been demonstrated to be an independent risk factor for severe lower respiratory

tract infections in infants.⁽²⁷⁾ These observations are consistent with the current evidence about the epidemiology and risk factors for respiratory disease in paediatric populations.^(26, 27, 34, 38, 88, 91) The significance of overall and within domain scores for the LRSQ will be better understood once all questionnaires have been received and fully analysed.

Over the next five years it is hoped that researchers will gain significant insight in to the natural history of respiratory symptoms in the Liverpool preschool population, and that the study will have a significant impact upon health promotion initiatives and social policy in the city of Liverpool. There is strong evidence that links social deprivation to respiratory disease within paediatric populations, however some may argue that other risk factors associated with deprivation, such as increased levels of prenatal and postnatal cigarette smoke exposure, lack of breast feeding, poor nutrition and poor air quality are confounding. However, one study that previously examined these risk factors successfully demonstrated that socioeconomic deprivation was an independent risk factor for severe respiratory tract infection during infancy, regardless of confounding factors.⁽²⁷⁾ The repeated longitudinal analysis of exposures to known risk factors for respiratory disease in the LRBCS will permit researchers to further explore the relationship between deprivation and respiratory disease in children. Furthermore, univariate and multivariate analysis of exposures and the severity of respiratory symptoms may also allow researchers to measure the size of effect as well as the relative risk of individual risk factors, including deprivation, and also gain further insight in to the relationship that exists between these factors. Cohort study design also permits for nested studies, which may allow researchers to understand whether migration to or from the city's most deprived areas increases the severity of new-onset or established respiratory disease in children. The study is currently in its infancy, but researchers believe that both the unique design and setting of the LRBCS will permit for the complex relationships between risk factors to become untangled, in turn allowing researchers and clinicians to identify the most at risk children, ultimately leading to primary disease prevention.

6.2 Strengths

Longitudinal observational studies like the LRBCS allow researchers to gain insight in to the relationship between a number of exposures and variables with a number of outcomes in individuals and populations over an extended period of time. The study design helps us understand the temporality of various disease processes, and how these process evolve over a number of years or a lifetime. Prospective studies that commence at birth minimise the effects of recall bias, as risks and exposures are continuously recorded as they occur.

A further strength of the LRBCS is its contemporary study design, where the latest technologies are used to maximise engagement with mothers, while keeping financial costs to a minimum. Children that move outside of eligible postcodes will continue to be followed up by the study, and using email addresses to distribute questionnaires may reduce the loss of cohort member to migration, which has been a significant issue in other cohorts.

6.3 Limitations

Despite the strengths and current success of the LRBCS, a number of factors exist that may ultimately limit the scope of the study. As previously discussed the exclusion of mothers who could not speak English and infants who were being taken in to the care of local authorities may affect population sampling in the study. However, due to the small size of the research team and limited availability of funding, these issues cannot be overcome. Issues with long term follow up of participants that migrate may also arise due to these factors.

This is a local population birth cohort study, thus the generalizability of results will be limited. Despite this, the effects of important risk factors such as household cigarette smoke and social deprivation upon respiratory symptoms in preschool children will be relevant regardless of geographical location.

Selection bias is an important factor that may affect the quality of results in any study population. Despite providing the majority of Liverpool city's maternity services, it must be considered that not all mothers of infants born in postcodes L1-L38 will deliver at LWH, as their homes may be geographically closer to one of the two district general hospitals in the region that also provide maternity services. Furthermore, it will not be possible to recruit mothers who opt for home births. LWH provides secondary and tertiary care, thus premature, or low birth weight infants, as well as multiple births and children with co-morbidities may be overrepresented in the sample. These demographics will be monitored during the initial questionnaire which will permit researchers to correct for these factors if necessary. The primary outcome measure of the questionnaire is an online questionnaire. It must be considered that this method of participation may not appeal to mothers from certain demographics. The research team have made efforts to limit this potential source of bias by offering postal options, and furthermore have offered to create a large print version of the questionnaire for one partially sighted mother.

Whilst the research team aims to recruit a large number of infants to the study, which will help increase the statistical power of results, this may also increase loss of

participants in follow up and attrition rates as it will become increasingly difficult for a small research team to manage the logistics of maintaining contact with large number of participants. Certain population groups may be more likely to not respond or leave the study, which may result of underrepresentation of these groups in the sample.

6.4 The future of the LRBCS

During the coming months, a new research student will join the LRBCS study team and will continue to personally recruit mothers to the study at LWH using the previously discussed methods. The distribution of the initial questionnaire to mothers when their child reaches age four months. In November 2013 the research team will commence distributing the first follow up questionnaire when the pilot group reach 10 months of age. This will be a crucial period for the study, as it will provide further insight in to the feasibility of the longitudinal follow up of infants.

The research team have received suggestions about using popular social media sites, such as Facebook Inc. and Twitter Inc. to raise the profile of the study. Other studies have experimented with using targeted advertisement to recruit via these sites, and some other cohort studies do have pages.^(172, 178, 235, 236) The Born in Bradford study had an exemplary Facebook page (<https://www.facebook.com/BornInBradford>), which involved events, advice and information and is highly engaged with the cohort.⁽⁶⁶⁾ Furthermore, Ninfea, the Italian cohort study that was conducted online has enrolled participants directly from social media sites.⁽²³⁷⁾ However, further research revealed that a number of social media pages for the majority of the studies were poorly maintained and had little or no engagement with the cohort. This can also raise issues surrounding participant confidentiality and professionalism, and any social engagement with participants must be performed with strict adherence to current guidelines.⁽²³⁸⁾ Therefore, as the responsibility for maintaining such pages would be changing regularly, the LRBCS research team decided it would not be wise to create a social media presence at this point.

A further role of the new research student will be investigating new methods of increasing response rates and reducing attrition. As previously mentioned, a smartphone application to complete the questionnaire, and the capacity for automated on-screen reminders is highly desirable. Furthermore, the research team have already commenced researching the possibility of using text messages as reminders, which would be a particularly cost- and time-effective method of reminding mothers who receive postal questionnaires to respond. Contact details held in the MailChimp® database can be used with TextMarketer®, a mass Short Message Service (SMS) sending software to resend

invitations or remind participants who have not yet completed the questionnaire. Using these reminders on a sample of 100 mothers from the pilot who had not responded to the initial invitation has so far yielded 6 questionnaire responses, and a further three mothers contacted the research team to communicate that they were no longer interested in participating in the study.

6.5 Recommendations

It is essential that recruitment to the study continues using the proven methods described in this thesis until at least January 2014. Future research students may consider slight alterations to the demographics and exposures questionnaires, including highest educational qualification, breastfeeding duration and smoking during pregnancy, to record data in a way that is precisely the same as data collected by censuses or other official statistics. This will make future analyses and comparisons of datasets more robust and reliable.

6.6 Conclusion

The LRBCS is a birth cohort study that explores the prevalence and impact of respiratory symptoms in children living in the city of Liverpool from birth until age five years. This will be achieved through the biannual assessment of symptoms using an online questionnaire that contains the LRSQ in addition to a demographics and exposure questionnaire. To date, the research team have obtained 1685 expressions of interest in the study, and 220 mothers have proceeded to complete the initial questionnaire and fully consent to participate in the study. The success of the LRBCS can be attributed to the development and design of the study, which was heavily influenced by the feedback and opinions of mothers.

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Appendix

1. Study Protocol Version 3.0

Version 1.0 of the study protocol was created by R Pickles and MG Semple in 2012. There have been some minor revisions since the original protocol.

Study Protocol

The Liverpool Respiratory Birth Cohort Study

A Prospective, Longitudinal Birth Cohort study using the Liverpool Respiratory Symptom Questionnaire to conduct a biannual assessment of the respiratory symptoms of preschool children born in Liverpool from birth until the age of five years.

Miss Rosanna Pickles
Miss Bethan Griffith
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Dr Kevin Southern
Professor Ben Shaw

Abstract

Objective: To describe respiratory symptoms of preschool children using the Liverpool Respiratory Symptom Questionnaire (LRSQ) from birth until the age of five years, in Liverpool by bi-annual assessment.

Method: Newborn infants will be recruited during their mother's stay at the Liverpool Women's Hospital (LWH). Prior to discharge, research students will provide information to mothers about the study in the form of a postcard. Mothers will be asked to fill in their contact details including email and phone number indicating their interest in taking part. Completion of the postcard implies consent to be contacted. Postcards may be deposited in collection boxes at the LWH. Once the research team have received the postcards, parents will later be sent an email or letter thanking for their interest in the study. When the baby is four months old an email will be sent to the mother, which will include an option to consent to take part and a link to the initial online questionnaire. Mothers may alternatively opt to receive the questionnaires by post. The questionnaire will then be emailed or posted to mothers six monthly until their child is five years old. Demographic details will be requested on initial enrolment and confirmed or updated during the course of the study. Data will be hosted on-line by Adobe Forms Central software in an encrypted and anonymized format and stored on secure servers at the University of Liverpool.

Analysis: Demographic, exposure and LRSQ data collected by Adobe Forms Central software, which is compatible with the statistical analysis software SPSS™. Univariate and multivariate analyses using linear regression analysis will be used to compare domain scores of the LRSQ scores with exposures/variables such as prematurity, birth weight, deprivation and exposure to cigarette smoke in pregnancy and in the household. Structural equation analysis and multinomial regression analysis will also be used to assess any relationship between exposure/demographic variables and respiratory symptoms. Cronbach's alpha coefficients will be calculated to assess internal validity.

Introductions

A literature search of birth cohort studies that explore respiratory symptoms revealed 129 studies conducted between 1961 and 2011 written in the English language. Of these 129 studies 17 separate respiratory birth cohort studies were identified. Among the UK studies identified are the AVON study using the Bristol cohort, the 'Children of the 1950's and the National Child development study. International studies specifically focusing on respiratory symptoms include the Tucson Cohort and the ISAAC study. All use a respiratory questionnaire to assess respiratory symptoms, but none assessed the impact of respiratory symptoms on both preschool children and their parents. The Liverpool Symptom Questionnaire (LRSQ) is specifically designed to assess the impact of respiratory symptoms on preschool children and their parents. This study is the first proposed birth cohort study to use the LRSQ.

Over the last few decades numerous questionnaires have been designed to explore the respiratory symptoms of adults and children. Many studies have since been conducted to examine the validity of these questionnaires. Questionnaires may be delivered by an interviewer, be completed by either the patient themselves or by the parent's of the patient. Self-completion questionnaires have proven to be more economical and also help reduce observer bias when compared to interview questions ¹⁸.

A literature search was conducted using Medline. Keywords searched include 'respiratory' 'symptom' and 'questionnaire'. The results were limited to the dates 1991 to 2011. In total 775 articles were identified and reduced to 69 after reviewing titles and abstracts to determine relevance. The 69 articles related to 36 different respiratory symptom questionnaires for both children and adults and enabled identification of the most commonly used questionnaires.

Questionnaires for respiratory symptoms commonly used in adults include the St George Respiratory Questionnaire (SQRQ), the American Thoracic Society

Standardized Respiratory Questionnaire (ATSq), the Global Allergy and Asthma European Network Questionnaire (GA2LENq) and the MRC respiratory symptom questionnaire. The most commonly used questionnaires in the studies identified are the SQRQ and modified versions of the ATSq. The primary symptoms explored using the questionnaires are cough, wheeze, and breathlessness. Many studies have edited existing questionnaires to include questions on smoking, occupational hazard and various other exposure or occupational respiratory hazards. The most commonly used questionnaire's available specifically for children include the ISAAC questionnaire for ages 6 years to 13 years, and the Test for Respiratory and Asthma Control in Kids (TRACK). Both questionnaires have been validated by numerous studies. Many of the adult questionnaires explore the impact of respiratory symptoms upon the patient. The St Georges Questionnaire for adults addresses the affect of respiratory symptoms upon patient but not upon the family. The Wisconsin Upper Respiratory Symptom Survey (WURSS 44) includes questions on whether the persons cold has affected their daily activities, work inside and outside their home, interact with others and personal life ¹⁹. The Living with Asthma Questionnaire explores the impact of asthma on the person completing the questionnaire, however this is a questionnaire designed for adults and is specific to Asthma and doesn't necessarily incorporate any other respiratory condition ²⁰.

As discussed many adult questionnaires explore the impact of respiratory symptoms upon the patient and their lives. However, currently no preschool questionnaire for parental completion explores the impact of these respiratory symptoms on the children and their parents. There are also very few respiratory questionnaires validated specifically for the preschool age groups and the LRSQ addresses both these issues.

The Liverpool Respiratory Score Questionnaire (LRSQ) is a validated tool that explores the prevalence of respiratory symptoms in infants and preschool children. This parental completion questionnaire was first designed using established criteria, as a follow up tool for use in neonatal studies where the outcome of children two to three years of age was of interest. A unique

feature of the LRSQ is that it also explores the impact of wheeze attacks and other respiratory symptoms upon the child and their family. The LRSQ consists of nine domains. Each domain contains between three and five questions seeking responses scored on a five point Likert scale from "not at all" (score 0) to "every day" (score 4). The first six domains assess respiratory symptoms such as wheeze and cough. The next two assess the effect on the child and their family. The final section asks for details regarding medication, GP/clinic visits, hospital admissions and labels given. All domains ask parents to consider symptoms/effect over the last three months.

Birth Cohort studies are an invaluable tool for studying the epidemiology of specific populations. This study aims to map the natural history of respiratory symptoms of preschool children born in the Liverpool. It is likely to be an invaluable tool to assess the complex relationships between childhood respiratory symptoms and deprivation, premature birth, birth weight, smoking in pregnancy and smoking by household members. Liverpool is recognised as being of the most deprived cities in the England with high rates of cigarette smoking ²¹. This permits for reliable studies into these effects and makes Liverpool an ideal location for a birth cohort study. The majority of births occur at one centre facilitating recruitment.

Work underpinning this study

Three studies have been conducted using the LRSQ. The first, by C V Powell et al (2002) developed and validated the standardised questionnaire ²². After reviewing other questionnaires we find that most do not explore the impact of specific respiratory symptoms, including wheeze, on the child and their family. However, the LRSQ does this well with two of 9 domains exploring the impact of respiratory symptoms on both the child and their family. A relatively small cohort was used for initial exploration of the questionnaire, however the authors justify this as a reasonable number, as other questionnaire used similar figures. After assessing particular areas such as response rates and reliability, the authors demonstrated that it is an acceptable questionnaire, easily completed, with good response rates ²². However they did not attempt to examine the readability in detail or looked at factors, which may affect responses ²².

The second was a cross sectional study that explores respiratory symptoms in Cystic Fibrosis ²³. This study also further validated the questionnaire's external and internal validity. The study showed that the LRSQ has good internal validity across 6/8 domains. It covered an extensive number of symptoms while also maintaining acceptability. It also demonstrated the LRSQ as a potential tool for assessing and monitoring respiratory symptoms in preschool children with cystic fibrosis.

A small, unpublished cross-sectional study has also been conducted using the Liverpool cohort, which used the LRSQ to explore respiratory symptoms in infants following exposure to RSV bronchiolitis. This study again demonstrated good internal validity using the Cronbach's coefficient but also enabled identification on small issues with the design of the questionnaire with the possibility of many improvements that may help with data collection and improve the clarity of the questionnaire.

Justification of this study

A literature search was conducted identifying birth cohort studies that feature a respiratory component. Among the UK birth cohort studies identified were the AVON study a large longitudinal birth cohort, which recruited over 14,000 pregnant mothers from the Bristol Cohort ²⁴. The 'Children of the 1950's' is a large study conducted on the Aberdeen cohort followed children born in the 1950's up until adult life. The British National Child Development Study (BNCDS) started in 1958 and recruited all births within one week in the UK. International studies specifically focusing on respiratory symptoms include the Tuscon Cohort and the International Study of Asthma and Allergy in Children (ISAAC) study. Both of these use a respiratory questionnaire to assess respiratory symptoms, but did not apply it in preschool children.

The LRSQ has demonstrated potential as a tool for assessing respiratory symptoms in preschool children. The validity and utility of the LRSQ have been assessed in two previous studies, demonstrating it to be a useful tool for assessing respiratory symptoms in preschool children however further

validation is required, using a larger cohort of patients. Many large birth cohort studies have been conducted in the UK and Internationally.

This is the first proposed prospective birth cohort study to use the Liverpool Respiratory Symptom Questionnaire. This study will enable a large range of information regarding respiratory symptoms of preschool children and other risk factors predisposing children to respiratory and related disease. It enables numerous future studies to be conducted using the data collected. It allows exploration of respiratory symptoms in relation to demographic details and details of exposure to risk factors which is particularly of interest in Liverpool, as it is considered to be one of the most socially deprived cities in the United Kingdom²¹.

Research Method

Study design

This is a longitudinal birth cohort study using the parent completed Liverpool Respiratory Symptom Questionnaire (LRSQ) to assess preschool children's respiratory symptoms from birth up until the age of five years old. This study will also provide the opportunity for additional cross-sectional studies to be conducted on the patient group recruited and the results gathered. It is important to note that there will be no specific interventions made by the study.

Setting: Children normally resident in Liverpool postcodes L1-38.

Recruitment

We propose a maximum recruitment strategy and aim to recruit as many infants born at the Liverpool Women's Hospital as possible from January 2013. Recruitment will be limited only to parents domiciled within the Liverpool postcodes L1-38.

Newborn infants will be recruited during their mothers stay prior to discharge from the Liverpool Women's Hospital. Research students will personally provide information to mothers about the study verbally and in the form of a postcard while the mothers are at the Liverpool Women's Hospital. Mothers will be asked to fill in their contact details including email and phone number indicating their interest in taking part. Completion of the postcard implies consent to be contacted. Mother's hospital stickers will also be attached to the postcard. In addition, the postcard will also include a QR(2D) bar code which mothers may scan using their smart phones. This QR code will direct participants immediately to an online version sign up version of the postcard.

Once completed, research students will collect the postcards. Alternatively mothers, midwives or volunteers at the Liverpool Women's Hospital may deposit the postcards in a collection box. Once the research team have received the postcards contact details will be uploaded to the database sorted on the University of Liverpool's secure server. Within a week, parents will be sent an email thanking for their interest in the study. The next point of contact will be when the baby is four months old. An email will be sent to the mother, which will include a link to the initial online questionnaire. This email will include; information about the study, consent, questions regarding demographic and exposure details and the LRSQ in a series of separate but easily understandable pages. Mothers may alternatively opt to receive the postal questionnaires, which will be first sent within a week of the baby being four months old.

Recruitment material will make no therapeutic promises, as this is only a descriptive study. The inclusion and exclusion criterion ensures that no one is unfairly excluded from the study. All data collected will be automatically deposited on a password database on a secure server in the University of Liverpool. Where parents have indicated that they would prefer hard copy (paper) correspondence, this will be sent with a stamped address envelope for return. The research student will enter this data by hand. Data will be imported into an SPSS database on a case-by-case basis.

Follow Up

Consent will be obtained when the initial questionnaire is sent, four months after birth. Following that, a second email will be sent six months later and every six months thereafter until the child is five years old. This repeat mailing questionnaire will provide an option for participants to update any contact details and will include demographic and exposure questions and the LRSQ questions.

In addition, on the date of their child's birthday, mothers will receive a personalised email thanking them for taking part in the study and wishing their child a happy birthday. In the case of no reply, two reminder emails will be sent and if no response this will be followed by one contact by telephone and one postal contact as email addresses and telephone numbers may have changed over time. Each contact attempt will be two weeks after previous attempts. For mothers without email addresses or access to computers, reminders will be made by telephone and mailed by post.

With each email sent, mothers will be given an option to sign up to updates regarding recruitment and reports on any preliminary findings. Families who move out of the area will be asked to continue their involvement. Contact will continue by email and telephone. The questionnaire will include an option to update place of residence among other details.

Data Collection

Data will be linked from the on-line Adobe Forms Central Survey software into a SPSS database on a case-by-case basis throughout the duration of the study. The data collected from postal questionnaires will be inputted into the online survey manually by and subsequently inputted into the database by the research student.

Inclusion criteria

All infants born at the Liverpool Women's hospital, including premature births, where parents are normally resident in Liverpool postcodes (L1-38) regardless of future residence.

Exclusion criteria

Neonates born to parents normally resident outside the Liverpool postcodes L1-38.

Babies born to non-English speaking parents.

Variables and Outcomes Measures**Aim**

To establish a population based longitudinal birth cohort study conducting a bi-annual assessment of respiratory symptoms of preschool children using the LRSQ from birth to the age of five in Liverpool.

Primary objective: To describe parent reported respiratory symptoms in a population based birth cohort followed longitudinally from birth to five years old using the LRSQ.

Secondary objectives: To examine any association between differences in respiratory symptoms in groups of preschool children with different social and environmental risk and protective factors.

Bias

To minimise withdrawals from the study patients will be given three reminders, two via email and one by telephone contact after initial email of the questionnaire.

Recall bias is not considered to be a problem, as the questionnaire requires parents to report respiratory symptoms in the last three months and this recall period has been validated for this questionnaire

In the three previous studies parents have not fully completed the questionnaire, which may introduce reporting bias. Using the online questionnaire may help, as software prompts parents to complete all questions and can give options for null responses rather than leaving 'blanks' on paper.

Demographics and Exposure Variables

2.1.2 Box 1. Demographics <ul style="list-style-type: none">• Sex of child• Age of child• Date of Birth• Postcode• Ethnicity of child• Gestation at birth• Birth Weight (kg or lb/oz)• Mother's highest qualification• Breastfeeding duration (weeks/months)	2.1.1 Box 2. Exposure variables <ul style="list-style-type: none">• Nursery Attendance• Persons sharing the child's bedroom• Number of siblings living in a household• Maternal smoking during pregnancy (any)• Smoking by any household member in the last 3 months regardless of location• Chronic co-morbidities• Family history of atopy
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Proposed Study Size

We plan a maximum recruitment strategy from the Liverpool Women's Hospital where there are approximately 8,000 births each year. We estimate that approximately one in four mothers will complete the postcard provided. The questionnaire currently has a 13% return rate therefore we expect approximately 260 patients to participate in the study each year. Comparison of demographic data for those participating with census data will allow a check for recruitment bias.

Statistical Methods

The results from questionnaires on Adobe Forms Central will be uploaded to SPSS and analysed using the SPSS Statistical software. Rolling cumulative data analysis will be performed for the duration of five years.

Univariate and multivariate analyses using linear regression analysis will be used to compare domain scores of the LRSQ scores with exposures such as maternal smoking etc. Fishers exact test will be used to determine whether there is any relation between two categorical variables. Structural equation analysis and multinomial regression analysis will also be used to assess any relationship between exposure/demographic variables and respiratory symptoms. Cronbach's alpha coefficients will be calculated to re-assess internal validity. In this study missing data is most likely to result from failure to respond.

Data Sources: Patient Demographic Service

Data will also be collected from linked hospital episode data.

Data management

Data will be collected from questionnaire answers via the Adobe Forms Central Software and linked directly to the programme SPSS for analysis.

Consent

Mothers providing their contact details on the study information postcard implies consent to be contacted. The consent of mothers of patients will be sought when the first questionnaire is emailed or posted to participants. Mothers who are willing to participate will click on the embedded link to the questionnaire will be directed to a screen detailing more information about the study. After reading this they will be given the option to either not to participate and unsubscribe to emails, to contact the research team with any queries or to consent by clicking a button online and inserting their initials. After consenting to take part, mothers will be directed to the questionnaire. Mothers who opted for the postal questionnaire will be asked to complete a consent form alongside the initial questionnaire.

Patients and parents of patients at participating practices have the opportunity to opt out of the scheme at registration and any point thereafter by either contacting the research team or clicking a button on the email sent containing the LRSQ. [In studies involving postal questionnaires where the burdens are

insignificant and sensitive topics are not involved, the REC will normal regard the return of the questionnaire as adequate evidence of consent (IRAS guidance 2012)].

Ethical Issues

This study received REC ethical approval by proportionate review on 08/05/2012.

REC Reference: 12/EM/0194

This study also received REC approval of minor amendments on the 08/11/2012.

This allowed use of the QR barcode on the postcard for recruitment and the use of a poster with the QR code for recruitment and advertisement of the study at the Liverpool Women's Hospital.

No physical intervention will take place. The LRSQ database will include a study ID but not direct identifiers. The study ID and contact details will be kept in an encrypted data file in a secure server hosted by the University of Liverpool. The survey has only been validated in an English Language format. There is no capacity in this student project to develop and validate the LRSQ in other languages.

Risks to Patient

There are few anticipated risks for research participants in this study. Possible risks include a breach in confidentiality with regards to contact details of patients and any personal data. Precautions will be taken to minimize the risk of this data will be stored very carefully. No identifiable data will be included in publications. Security data measures that will be taken include encrypting data with passwords, coding medical conditions and limiting access to study data.

An additional foreseeable risk identified is the risk of sending emails and questionnaires to parents of deceased children. Measures that could be taken

include linking to the National mortality database via the Patient Demographic Service. The Alder Hey Children's NHS Foundation Trust's IT department will perform weekly batch searches linking to SPINE via the Patient Demographic Service. This, however, is not a foolproof method as there will be delays between the PDS being notified by the community and by Alder Hey Children's Hospital.

Benefits to patients

There are no direct benefits to research participants taking part in this study. However there we hope that this study will benefit future preschool children by enabling us to identify risk factors associated with particular respiratory symptoms.

Risks / benefits to study

If too few participants are recruited this would compromise the results of the study. There is also the risk of losing patients to long-term follow-up. If patients are lost the data will still be included in the results.

Research governance

The University of Liverpool will be lead sponsor and the Liverpool Women's NHS Foundation Trust will co-sponsor for the study.

The proposed study will be undertaken in accordance with the University of Liverpool's research governance procedures.

Dr MG Semple (Liverpool University), Professor Ben Shaw (Liverpool Women's) will be a joint guarantor for analysis and reports.

The Research Team

Miss Rosanna Pickles

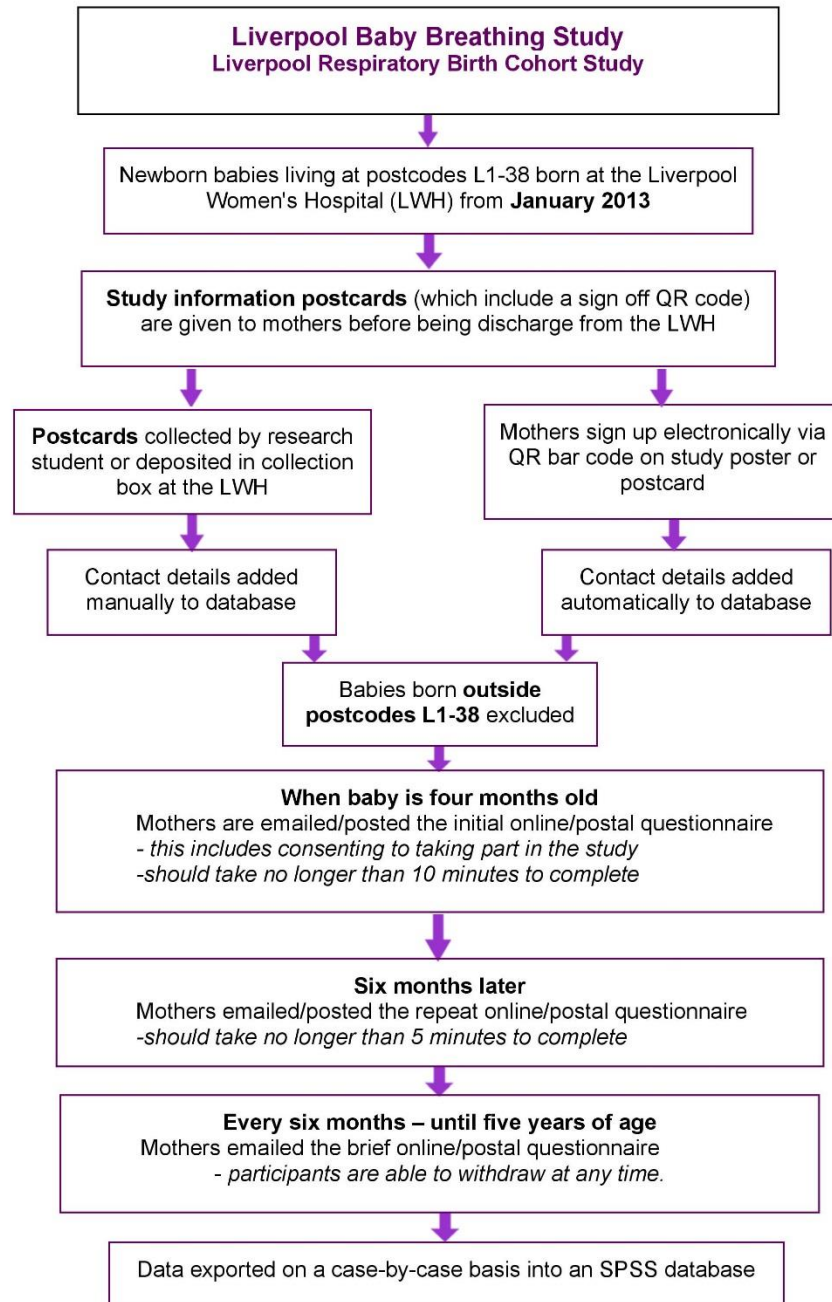
Miss Bethan Griffiths

Dr MG Semple (Chief Investigator)

Professor Ben Shaw

Dr Kevin Southern

Dr Paul McNamara



Timetable and Milestones

Phase One – completion of protocol and application to IRAS for ethical approval by May 2012

Phase Two – Development of the online questionnaire and consent form. Prior to the start of the study mothers will be interviewed regarding questionnaire aesthetics. Once the questionnaire design has been finalised the questionnaire will then be trialed at the Liverpool Women's hospital. Mothers will be interviewed while they are completing the questionnaire about the design, layout, format and content of questions; ease of use and asked to score the questionnaire out of ten. Mothers will also be asked about anything that would motivate them to participate in the study, and encourage continued participation.

Phase Three – Recruitment of mothers and implementation of the study will begin on the 7th January 2013 and continue for a maximum of five years depending on the success of the study. The study will continue for a further five years after recruitment is complete.

Expertise

- Dr MG (Calum) Semple is a Senior Lecturer in Child Health at the University of Liverpool and Consultant in Paediatric Respiratory Medicine at Alder Hey Children's Hospital.
- Professor B Shaw, Consultant in Neonatal and Respiratory paediatrics at Liverpool Women's Hospital and the Royal Liverpool Children's Hospital.
- Dr Paul McNamara, Senior Lecturer in Child Health at the University of Liverpool and Consultant in Paediatric Respiratory Medicine at Alder Hey Children's Hospital
- Dr K Southern Reader in Paediatric Respiratory Medicine at the University of Liverpool and Consultant in Paediatric Respiratory Medicine at Alder Hey Children's Hospital

Service Use Input

Mothers of the participants will be involved in the development of the study, particularly with the development of the postcard information card and also the design, content and format of the online questionnaire. Research students will interview mothers at the Liverpool Women's Hospital about the aesthetics and format of the questionnaire and postcard. Finalised versions of the questionnaire will be piloted at the Liverpool Women's Hospital. Mothers will be interviewed while completing the online questionnaire. Interview questions will be standardised and prepared prior to seeing the parent. They will be asked to feedback on matters such as appearance and format, ease of completion, and clarity and content of the information and questions.

References

1. Attfield MD. Respiratory Questionnaires.
2. B. Barrett REB, M. P. Mundt, G. R. Thomas, S. K. Barlow, A. D. Highstrom, and M. Bahrainian. Validation of a short form Wisconsin Upper Respiratory Symptom Survey (WURSS-21). *Health and Quality of Life Outcomes*. 2009;7.
3. Living with Asthma Questionnaire. Available from: <http://www.psy.plymouth.ac.uk/research/mhyland/Scoring%20the%20Living%20with%20Asthma.pdf>.
4. The English Indices of Deprivation 2010.
5. Powell CVE, McNamara P, Solis A, Shaw NJ. A parent completed questionnaire to describe the patterns of wheezing and other respiratory symptoms in infants and preschool children. *Archives of disease in childhood*. 2002 November 1, 2002;87(5):376-9.
6. R Trinick KS, P McNamara. Assessing the Liverpool Respiratory Symptom Questionnaire in Children with Cystic Fibrosis. 2011.
7. Children ALSoPa. Avon Longitudinal Study of Parents and Children. University of Bristol; 2012; Available from: <http://www.bristol.ac.uk/alspac/>.

2. Search Strategy for LRBCS Review of Literature

A systematic review of literature relevant to the LRBCS was performed between the months of February and June 2013 using the National Centre of Biotechnology Information PubMed search tool. The objectives of the systematic review were to identify key literature relating to;

- 1) Significant Birth Cohort Studies (International, National, Regional and Local Studies)
- 2) Significant paediatric respiratory studies(International, National, Regional and Local Studies)
- 3) Respiratory Symptom Questionnaires (General/Adult and Paediatric)

References from relevant papers were also searched in order to identify any further

relevant
studies

#	Search Terms	Results
1	Birth cohort study	48607
2	British birth cohort study	967
3	Birth cohort	23710
4	Respiratory birth cohort study	3894
5	Paediatric respiratory study	9322
6	Respiratory symptom study	37085
7	Respiratory symptom study children	6167
8	Respiratory symptom study paediatric	2309
9	Longitudinal study birth	26063
10	Asthma birth cohort	1252
11	Longitudinal study children	170737
12	Respiratory questionnaire	13989
13	Respiratory symptom questionnaire	4976
14	Paediatric respiratory symptom questionnaire	291
15	Paediatric respiratory questionnaire	843
16	Respiratory AND birth AND cohort	1764
17	Respiratory AND children AND cohort	3707
18	Paediatric AND respiratory AND questionnaire	843
19	Longitudinal AND study AND children	28186
20	Liverpool respiratory	842
21	Merseyside respiratory	54
22	Liverpool respiratory children	248
23	Merseyside respiratory children	23

3. Version 1.0 of the Liverpool Respiratory Symptom Questionnaire

Respiratory Questionnaire

Study No :

Date

Name :

Sex : male female (please circle)

Date of birth :

Place of birth :

Age (weeks) :

Address :

.....

.....

Telephone no :

The following questionnaire asks questions about your child and what has been happening to him/her over the last three months.

Please could you fill in the questionnaire by putting a circle around your response to each question.

It is important that every question is answered, even if your child has been perfectly well, with no problems at all.

Thank you.

Copyright Liverpool Womens Hospital

Name of Child

Study Number

1. This first question refers to at any time in your child's life:

Has your child ever had wheezing (whistling noise coming from the chest) at <u>any time in the past</u> ?	<i>Yes</i>	<i>No</i>
---	------------	-----------

2. The next questions are specifically aimed at the last three months:**A) During the day (when awake) in the last three months:**

i) My child has had wheezing (whistling noise coming from the chest):

<i>Every day</i>	<i>most days</i>	<i>some days</i>	<i>a few days</i>	<i>not at all</i>
------------------	------------------	------------------	-------------------	-------------------

ii) My child has had a cough:

<i>Every day</i>	<i>most days</i>	<i>some days</i>	<i>a few days</i>	<i>not at all</i>
------------------	------------------	------------------	-------------------	-------------------

iii) My child has had a rattly chest:

<i>Every day</i>	<i>most days</i>	<i>some days</i>	<i>a few days</i>	<i>not at all</i>
------------------	------------------	------------------	-------------------	-------------------

iv) My child has been short of breath:

<i>Every day</i>	<i>most days</i>	<i>some days</i>	<i>a few days</i>	<i>not at all</i>
------------------	------------------	------------------	-------------------	-------------------

B) During the night (when asleep) in the last three months :

i) My child has had wheezing (whistling noise coming from the chest):

<i>Every night</i>	<i>most nights</i>	<i>some nights</i>	<i>a few nights</i>	<i>not at all</i>
--------------------	--------------------	--------------------	---------------------	-------------------

ii) My child has had a cough:

<i>Every night</i>	<i>most nights</i>	<i>some nights</i>	<i>a few nights</i>	<i>not at all</i>
--------------------	--------------------	--------------------	---------------------	-------------------

iii) My child has had a rattly chest:

<i>Every night</i>	<i>most nights</i>	<i>some nights</i>	<i>a few nights</i>	<i>not at all</i>
--------------------	--------------------	--------------------	---------------------	-------------------

iv) My child has been short of breath:

<i>Every night</i>	<i>most nights</i>	<i>some nights</i>	<i>a few nights</i>	<i>not at all</i>
--------------------	--------------------	--------------------	---------------------	-------------------

v) My child has snored :

<i>Every night</i>	<i>most nights</i>	<i>some nights</i>	<i>a few nights</i>	<i>not at all</i>
--------------------	--------------------	--------------------	---------------------	-------------------

Study Number

<i>None</i>	<i>one</i>	<i>two</i>	<i>three</i>	<i>more than three</i>	<i>always has a cold</i>
-------------	------------	------------	--------------	----------------------------	----------------------------------

When my child has had a COLD in the last three months:

<i>Every cold</i>	<i>most colds</i>	<i>some colds</i>	<i>a few colds</i>	<i>not at all with colds</i>
-------------------	-------------------	-------------------	--------------------	------------------------------

<i>Every cold</i>	<i>most colds</i>	<i>some colds</i>	<i>a few colds</i>	<i>not at all with colds</i>
-------------------	-------------------	-------------------	--------------------	------------------------------

<i>Every cold</i>	<i>most colds</i>	<i>some colds</i>	<i>a few colds</i>	<i>not at all with colds</i>
-------------------	-------------------	-------------------	--------------------	------------------------------

Every cold most colds some colds a few colds not at all with colds

<i>Every day</i>	<i>most days</i>	<i>some days</i>	<i>a few days</i>	<i>not at all</i>
------------------	------------------	------------------	-------------------	-------------------

<i>Every day</i>	<i>most days</i>	<i>some days</i>	<i>a few days</i>	<i>not at all</i>
------------------	------------------	------------------	-------------------	-------------------

Every day	most days	some days	a few days	not at all
-----------	-----------	-----------	------------	------------

Every day	most days	some days	a few days	not at all
1	2	3	4	5

Name of Child

Study Number

E) When my child has been MORE ACTIVE (e.g. crawling, walking or when excited) in the last three months:

i) My child has had wheezing (whistling noise coming from the chest):

Every day most days some days a few days not at all

ii) My child has coughed:

Every day most days some days a few days not at all

iii) My child has had a rattly chest:

Every day most days some days a few days not at all

iv) My child has been short of breath:

Every day most days some days a few days not at all

F) These next three questions are about other problems your child may have had. Over the last three months:

i) My child has had noisy breathing that does not seem to come from the chest :

Every day most days some days a few days not at all

ii) My child has had fast breathing:

Every day most days some days a few days not at all

iii) My child has had noisy breathing that appears to come from the throat or back of the throat:

Every day most days some days a few days not at all

Name of Child

Study Number

G) The next four questions are on how your child's chest symptoms actually affect HIM or HER over the last three months:

i) My child's chest symptoms have affected my child's feeding or eating:

Every day most days some days a few days not at all

ii) My child's chest symptoms have woken up my child:

Every night most nights some nights a few nights not at all

iii) My child's chest symptoms have reduced my child's activity:

Every day most days some days a few days not at all

iv) My child's chest symptoms have made my child unusually tired:

Every day most days some days a few days not at all

H) The next four questions are on how your child's chest symptoms actually affect YOU and YOUR family's life the last three months:

i) My child's chest symptoms have limited my activities:

Every day most days some days a few days not at all

ii) My child's chest symptoms have resulted in adjustments being made to our family life:

Every day most days some days a few days not at all

iii) My child's chest symptoms have disturbed our sleep:

Every night most nights some nights a few nights not at all

iv) I have been worried about my child's chest symptoms:

Every day most days some days a few days not at all

4. Demographics and Exposures measured in the LRBCS

Demographics

- Sex of child
- Age of child
- Date of Birth
- Postcode
- Ethnicity of child
- Gestation at birth
- Birth weight (grams)
- Maternal Smoking during pregnancy
- Mothers highest qualification
- Family history of atopy

Exposures

- Nursery Attendance
- Breastfeeding duration in weeks
- Number of persons per room
- Number of siblings in household
- Siblings sharing a room with child
- Any household smoking during pregnancy regardless of location (specify)
- Smoking by any household member in last 3 months regardless of location (specify).
- Chronic co-morbidities.

5. Presentation used in the initial patient and public involvement session at Liverpool Women's Hospital, July 2012



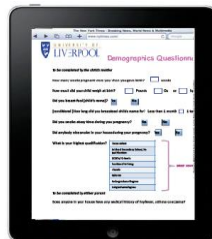
Liverpool Respiratory Birth Cohort Study

Pilot

What would be the most convenient way for you to complete a questionnaire?



Laptop or PC



Tablet



Smart Phone

To which (if any) of these devices do you have access?




Layout:

How do you prefer the information to be presented to you?

All the information/questions on one page?

A few similar questions grouped together over a few pages?

One question per page?



1. This first question refers to at any time in your child's life:

Has your child ever had wheezing (whistling noise coming from the chest) at any time in the past?

Please select
Yes
No

2. The next questions are specifically aimed at the last three months:

A) During the day (when awake) in the last three months:

i) My child has had wheezing (whistling noise coming from the chest):

ii) My child has had a cough:

iii) My child has had a rattly chest:

iv) My child has been short of breath:

B) During the night (when asleep) in the last three months :

i) My child has had wheezing (whistling noise coming from the chest):

ii) My child has had a cough:

iii) My child has had a rattly chest:

iv) My child has been short of breath:




v) My child has snored :

Next

Done: 37%

1

Densely filled so you can see all the questions?



B) During the night (when asleep) in the last three months :

i) My child has had wheezing (whistling noise coming from the chest):

ii) My child has had a cough:

iii) My child has had a rattly chest:


iv) My child has been short of breath:

v) My child has snored :

Done: 37%

A few questions at a time so it's manageable?

2



7. The next four questions are on how your child's chest symptoms actually affect HIM or HER over the last three months:

a. My child's chest symptoms have affected my child's feeding or eating:

Please select:
Every day
most days
some days
a few days
not at all

Done: 37%

One question at a time so you can think properly about each one?

3

Format

What kind of background appeals to you the most?

Plain

Images

Coloured

Patterns

White

Would you prefer a page to be colourful, or does a more neutral format appeal to you more?



The LRSQ



B) During the night (when asleep) in the last three months :

i) My child has had wheezing (whistling noise coming from the chest):

ii) My child has had a cough:



iii) My child has had a rattly chest:

iv) My child has been short of breath:

v) My child has snored :

1

....A plain and simple page with only the relevant text?



The LRSQ

B) During the night (when asleep) in the last three months :

i) My child has had wheezing (whistling noise coming from the chest):

ii) My child has had a cough:



iii) My child has had a rattly chest:

iv) My child has been short of breath:

v) My child has snored :

....Quite plain but with a little colour in the background?

2a



The LRSQ

B) During the night (when asleep) in the last three months :

i) My child has had wheezing (whistling noise coming from the chest):

ii) My child has had a cough:

iii) My child has had a rattly chest:


iv) My child has been short of breath:

v) My child has snored :

A tiny bit of colour?

2b

5.
6



Liverpool Women's
NHS Foundation Trust
Dedicated to you

Liverpool Respiratory Symptom Questionnaire

6. These next three questions are about other problems your child may have had.

Over the last three months:

a. My child has had noisy breathing that does not seem to come from the chest :

b. My child has had fast breathing:

c. My child has had noisy breathing that appears to come from the throat or back of the throat:

NEXT

Plain but with different or unusual fonts?

Progress

32 %

Themes, Images and Logos

Do you prefer a “grown-up” or child friendly design?

Do colours and pictures tend to keep your attention?

...or do you find them distracting?

Do you get bored when looking at black and white pages of questions?

Would pictures or colours make you likely to carry on with the questionnaire longer than a plain one?

Considering the purpose of this questionnaire, are themes relating to childhood relevant?

9.
10.



6. These next three questions are about other problems your child may have had.

Over the last three months:

a. My child has had noisy breathing that does not seem to come from the chest :



b. My child has had fast breathing:

c. My child has had noisy breathing that appears to come from the throat or back of the throat:

Something colourful that brightens the page without taking over?



1



Liverpool Respiratory Symptom Questionnaire

6. These next three questions are about other problems your child may have had.


Over the last three months:

a. My child has had noisy breathing that does not seem to come from the chest :

b. My child has had fast breathing:

c. My child has had noisy breathing that appears to come from the throat or back of the throat:

A subtle theme that brings everything together?



2

11.

12.

UNIVERSITY OF LIVERPOOL

Liverpool Women's NHS Foundation Trust
dedicated to you

The LRSQ

6. These next three questions are about other problems your child may have had.
Over the last three months:

a. My child has had noisy breathing that does not seem to come from the chest :

b. My child has had fast breathing:

c. My child has had noisy breathing that appears to come from the throat or back of the throat:



Lots of bright colours?

3

Font size

How important is the size of the text?

Do you find larger text overwhelming or easier to read?



The LRSQ

6. The next three questions are about other problems that your child may have had.

Over the LAST THREE MONTHS:

1

- a. My child has had noisy breathing that does not seem to come from the chest Please select
- b. My child has had fast breathing Please select
- c. My child has had noisy breathing that seems to come from the throat or the back of the throat. Please select

The LRSQ

6. The next three questions are about other problems that your child may have had.

Over the LAST THREE MONTHS:

2

- a. My child has had noisy breathing that does not seem to come from the chest Please select
- b. My child has had fast breathing Please select
- c. My child has had noisy breathing that seems to come from the throat or the back of the throat. Please select

The LRSQ

6. The next three questions are about other problems that your child may have had.

Over the LAST THREE MONTHS:

3

a. My child has had noisy breathing that does not seem to come from the chest

b. My child has had fast breathing

c. My child has had noisy breathing that seems to come from the throat or the back of the throat.

Do you have any questions or suggestions about what you have been shown today?

THANK YOU!

6. Types of Questions that can be used to collect data

1. Single Line Text Field: one line of text can be entered

Freely entered text...

2. Multi Line Text Field: multiple lines of text can be entered

Freely entered text...

3. Date Field: Only valid dates can be entered

Aug 2013

Mo	Tu	We	Th	Fr	Sa	Su
			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31	

4. Email Field: Only valid with "@" symbol

person@email.com

5. Single Choice Field: A series of radio buttons permitting one answer only to be selected

- ☒ Answer 1
- ☐ Answer 2
- ☐ Answer 3

6. Multiple Choice Field: Radio buttons permitting multiple answers to be selected

- ☒ Answer 1
- ☐ Answer 2
- ☒ Answer 3

7. Drop Down Menu: A list of answers that drop down and can be scrolled

Answer 1

8. Matrix Question: A table where one or multiple responses may be selected to a number of questions or conditions

	Question 1	Question 2	Question 3
Answer 1	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>
Answer 2	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Answer 3	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>

7. Request for Support Document (Griffith and Pickles 2012)

17/10/2012

Request for Support

The Liverpool Respiratory Birth Cohort Study

*Miss Rosanna Pickles
Miss Bethan Griffith
Dr Calum Semple
Dr Kevin Southern
Professor Ben Shaw*

Introduction

The Liverpool Respiratory Birth Cohort Study (LRBCS) is a prospective, longitudinal birth cohort study that will use the Liverpool Respiratory Symptom Questionnaire (LRSQ) to conduct a biannual assessment of the respiratory symptoms of preschool children in Liverpool from birth to the age of 5. The LRSQ is a self-administered questionnaire for parents to complete. It has been pre-validated for use in this age group^{1,2}, and will be used alongside an exposures questionnaire to explore the prevalence and natural history of respiratory symptoms using eight key domains.

Rationale

There have been several international studies that have used questionnaires to assess respiratory symptoms and their impact in adults^{3,4,5}, and furthermore, there have been birth cohort studies in the United Kingdom that have contained respiratory elements⁶. Although some adult questionnaires explore the impact of these symptoms upon quality of life, as yet, no study has described the impact of respiratory illness in a preschool population. It is this assessment of both the prevalence and impact of such symptoms on this specific population and their parents that make the LRBCS a unique and valuable study. This study is the first proposed birth cohort study to use the aforementioned LRSQ.

Liverpool is recognised as being one of the most deprived cities in England⁷, with high rates of cigarette smoking. This permits for reliable studies into these effects and makes Liverpool an ideal location for a birth cohort study. The majority of births occur at the one centre facilitating recruitment, which is the largest single site maternity hospital in Europe⁸.

Ethics

This is an observational study, and thus there will be no specific interventions made by the study. The study was approved by the National Research Ethics Committee on 8th of May (REC ref: 12/EM/0194).

Aims

This study aims to map the natural history of respiratory symptoms of preschool children born in Liverpool.

Primary Objectives: To describe parent reported respiratory symptoms in a population based birth cohort followed longitudinally from birth to five years old using the LRSQ.

Secondary Objectives: To examine any association between differences in respiratory symptoms in groups of preschool children with different social and environmental risk and protective factors.

Methods

This is a longitudinal birth cohort study that will use the parent completed Liverpool Respiratory Symptom Questionnaire to assess the prevalence and impact of respiratory symptoms in preschool children living in Liverpool.

Recruitment

The study will employ a maximum recruitment strategy - all infants born to parents domiciled within the Liverpool postcodes, L1-L38 born at the Liverpool Women's Hospital born from January 2013 will be invited to join the study. Mothers of eligible newborns will be provided with an invitation postcard during their admission. The postcard will contain relevant information about the study, and will include a space to for parents provide contact details and basic information about their newborn. Completion of the postcard will register their interest in participating in the study, and imply consent to be contacted. Completed postcards will be deposited in a designated collection box on the ward, which will be emptied on a monthly basis by a member of the research team. Alternatively, parents may register their interest in the study by completing an online form accessible by scanning a QR code on the postcard or A4 Posters using their smartphone. These on-line forms are directly linked to the study database, and the technology allows for notifications to be sent directly to the research team when details are submitted online. Information posters will be displayed in relevant areas of the Liverpool Women's hospital to generate more interest in the study. Posters will also contain the QR code for online registration.



Contact information from the online form and postcards will be collated on a secure server to form a database. An initial mailing will be sent by secure email to parents when their infant reaches 4 months of age, thanking them for their interest in the study. The email will be personalised using a mail merge to contain the mothers name, a unique study ID, and will specify the first name of the child that will potentially be involved in the study. Inclusion

of the child's name will minimise confusion if the mother has other children, or if the child is a twin. The mail will contain a link to an encrypted webpage containing the questionnaire.

After clicking on the link within the email, parents will be taken to a welcome page, which contains important information regarding the study, and allows parents to either agree to participate and provide consent, ask for further information, or decline. Parents will be reminded that a decision not to participate will not affect the future care of themselves or their families.

Box 1. Demographics

- Sex of child
- Date of Birth
- Postcode
- Ethnicity of child
- Gestation at birth
- Birth Weight
- Mother's highest qualification
- Breastfeeding duration

Box 2. Exposure variables

- Nursery Attendance
- Persons sharing the child's bedroom
- Number of siblings living in a household
- Maternal smoking during pregnancy
- Smoking by any household member regardless of location
- Chronic co-morbidities
- Family history of atopy

If the parent consents, they will proceed to the main questionnaire. The initial questionnaire will include a demographics questions (see box 1), and will also ask questions about exposures (see box 2), and include an online version of the LRSQ for completion. Parents will be asked to confirm their contact details at the end of the questionnaire. Following the completion of the questionnaire, parents will receive a submission receipt by email, in which they will be thanked for their participation. Participants will also be given the opportunity to sign up receiving a supplementary newsletter that will contain updates from the Liverpool Respiratory Birth Cohort Study.

Parents will receive the next questionnaire 6 months later, when their infant is 10 months old. This questionnaire will contain the exposure questions and the LRSQ, as will each subsequent mailing –see email schedule in box 3. A “Happy Birthday” email will also be sent to parents on their child's birthdays whilst they are involved in the study. The mailing will also provide parents with the opportunity to update their contact details, or to opt in to the newsletter that provides general updates about the study. These methods aim to maintain communication and establish a relationship with the parents involved in the study, and it is hoped that this will encourage retention.

This scheduling of questionnaires, paired with a unique identification number for each child, will collect longitudinal data from the cohort, and will describe how the respiratory symptoms of preschool children in Liverpool evolve over time, in terms of both prevalence and impact.

Box 3. Email Schedule from sign up to end of study

1. **Immediately after sign up:** Welcome/ Thank you for your interest email – sent immediately after they sign up online, or as soon as we receive their details – will tell them we will be in touch when baby is 4 months old.
2. **4 Months:** Email link to [form 1](#) that contains: consent, further information, demographics, exposures, LRSQ. Also allow them to subscribe to updates from study.
3. **10 Months:** Email link to [form 2](#) that contains: exposures + LRSQ – check no changes to details at end. Also allow them to subscribe to updates from study.
4. **12 Months:** *Happy 1st Birthday email* – congratulate. Check that details have not changed, tell them we will be in touch with another questionnaire in 4 months time. Also allow them to subscribe to updates from study.
5. **16 Months:** Email link to [form 3](#) that contains exposures + LRSQ – check no changes to details at end. Also allow them to subscribe to updates from study.
6. **22 Months:** Email link to [form 4](#) that contains exposures + LRSQ – check no changes to details at end. Also allow them to subscribe to updates from study.
7. **24 Months:** *Happy 2nd Birthday email* – congratulate. Check that details have not changed, tell them we will be in touch with another questionnaire in 4 months time. Also allow them to subscribe to updates from study.
8. **28 Months:** Email link to [form 5](#) that contains exposures + LRSQ – check no changes to details at end. Also allow them to subscribe to updates from study.
9. **34 Months:** Email link to [form 6](#) that contains exposures + LRSQ – check no changes to details at end. Also allow them to subscribe to updates from study.
10. **36 Months:** *Happy 3rd Birthday email* – congratulate. Check that details have not changed, tell them we will be in touch with another questionnaire in 4 months time. Also allow them to subscribe to updates from study.
11. **40 Months:** Email link to [form 7](#) that contains exposures + LRSQ – check no changes to details at end. Also allow them to subscribe to updates from study.
12. **46 Months:** Email link to [form 8](#) that contains exposures + LRSQ – check no changes to details at end. Also allow them to subscribe to updates from study.
13. **48 Months:** *Happy 4th Birthday email* – congratulate. Check that details have not changed, tell them we will be in touch with another questionnaire in 4 months time. Also allow them to subscribe to updates from study.
14. **52 Months:** Email link to [form 9](#) that contains exposures + LRSQ – check no changes to details at end. Also allow them to subscribe to updates from study.
15. **58 Months:** Email link to [form 10](#) that contains exposures + LRSQ – check no changes to details at end. Also allow them to subscribe to updates from study.
16. **60 Months:** *Happy 5th birthday email* – congratulate. Thank them for participation and clarify that there will be no more questionnaires. Ask if they would still like to receive updates for the study.

Each email will be generated to contain: Parent's name, Child's name, Unique study ID of the child. Technology also allows us to add the address and telephone number that we currently hold for them (in case it needs to be changed).

Work to Date

To date, the focus of work around this study has been to maximise its appeal to mothers. Input from members of the target population during the development stages of the study is invaluable, and is practical and constructive⁹ – evidence shows that the aesthetics of a survey is crucial in maximising responses and thus yielding the best results^{10,11}. By involving mothers in the development of the study, the research team has been able to tailor the overall appearance and feel of the questionnaire to meet the preferences of women from the target population. Domains of questionnaire appearance that were explored with mothers included the use of background colours, images, logos, font style and size as well as the density of information. Furthermore, the research team have also explored whether parents were likely to prefer receiving a questionnaire by post or email- which reaffirmed the decision to conduct the LRBCS online.

Software

To ensure the success of the LRBCS, survey software needs to be acceptable in terms of freedom to design and usability for researchers. Software that has the scope to edit all elements of design and appearance is essential. The research team trialled several different products for survey or form building, but many of these were excluded on the basis of price, usability, security and post-purchase support (see box 4). Four possible software options were explored further; a comparison of which can be seen below in table 1.

Box 4. Survey building software tested

- Surveys: SelectSurvey.NET, Survey Monkey, Survey methods, Smart-Survey, Qualtrics (and Surveyz), Survey Expressions, KwikSurveys, SurveyBuilder, Survey Gizmo.
- Forms: Google Docs, Adobe FormsCentral, Wufoo, Formsite, WordPress FormBuilder, EmailMeForm.

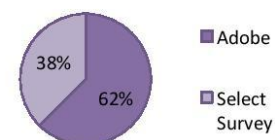
Table 1. Software Comparison

	Select Survey	Google Docs	Adobe Forms	Survey Monkey
Price (annually)	University funded	Free	£105.39	£299
Usability	Fair	Good	Excellent	Good
Appearance formatting	Colour	Templates	Unlimited	Templates
Skip Logic - question	No	No	Yes	Yes
Question Piping	Yes	No	No	Yes
Answer Pre-Population	No	No	No	Some
Help text	No	Limited	Yes	No
Logos and / images	1	No	Unlimited	1
Field Validation	Yes	No	Yes	Yes
Integrated email	Limited	No	No	Limited
Security System	Encrypted	Data cloud	SSL encryption	SSL Encryption
Statistical analysis	SPSS export	Excel export	SPSS export	SPSS export
Data Export	Yes	Yes	Yes	Yes
Data Summary	Yes	Yes	Yes	Yes
Progress Bar	Yes	No	Yes	Yes
Telephone/Email Support	Via University	No	Both	Email

After comparison of the software, the research team decided that the best options would be either SelectSurvey.NET, which was secure and available free through the University of Liverpool, but had some limitations in terms of formatting, or Adobe Forms Central, which is very easy to use and modify, but has moderate cost implications.

Both software options have their benefits and limitations. It was therefore decided that the most appropriate method to distinguish which should be used for the study would be by conducting a feasibility study at Liverpool Women's hospital. Versions of the initial mailing were created with identical questions and wording using the two software options. Mothers of newborn infants were approached on the maternity wards and asked to complete both versions of the questionnaire, and then asked to provide feedback on several aspects of both versions of the questionnaire, and finally to indicate which version they preferred. The order in which the two different versions were distributed to participants was alternated between patients to minimise bias. The results of this small feasibility study are illustrated in box 5. Of the sixteen women who participated, ten indicated that they preferred the Adobe software over the Select Survey Software.

Box 5.
Software Preference
n=16



Email

None of the survey software options that the research team explored had an integrated email system that would be suitable for the LRBCS. Although some of the mailing requirements of the study could be met with a simple email merge, this would require date calculations to be entered manually for each participant. The study has a maximum recruitment strategy, and thus potentially 8,000 participants per year; this is not practical and could result in human error leading to surveys being sent at incorrect dates. This system would also rely upon an individual's personal computer being switched on at the specified date and time, which is also highly impractical. After researching mail list management services, it was decided that MailChimp would be the most economical system to meet the needs of the study.

This service hosts email lists on a secure online server, and offers two-tiered security at no extra cost. The fully-automated service can schedule emails from the information held in its database – thus allowing for all future mailings to be set up at the initial sign up, without the need to calculate dates. A member of the research team can easily set up all future emails to be sent at specific intervals from a date held in the database, such as the child's date of birth, thus ensuring invitations for survey completion are deployed at precisely the correct time to the correct participants.

The service will also allow the research team to track whether individual participants have opened emails, and whether the link to the survey been opened. It also expresses the overall "open-rate" as a percentage. These features will allow the team to recognise poor response rates or any increases in drop-out, and will therefore allow them to address the root of these issues promptly.

MailChimp will allow recipients to easily exercise autonomy by removing themselves from the email list, which indicates to the research team that a participant would like to remove themselves from the study. This addresses the right of the participant to withdraw from the study at any time, consistent with the ethical approval obtained. Reports can be sent in real-time or on a daily basis to the research team detailing which participants have removed themselves from the study, again identifying the research team to identify problems promptly. If desired, the technology will allow the research team to ask participants to specify why they want to leave the study.

MailChimp will allow the research team to create emails using the same branding as the survey, using the Liverpool Women's Hospital and University of Liverpool logos, which will give the emails a professional branded appearance that hopefully will be recognised instantly by participants. There are unlimited merge fields, which allow the research team to

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personally address the email to parents, and contain the name of their child and the unique identification number. Replies to these automated emails will be sent directly to the research teams' email address.

Request for support

The study will be conducted over a minimum of 6 years. Recruitment will take place during the first year of the study, and children will be followed up biannually until the last child to be recruited has reached his or her fifth birthday.

Prior to the research team commencing with recruitment, financial support is required for the survey software, mailing system, and also the printing of postcards.

Software

Item Requested: Adobe Forms Central subscription@ £105.39/year [for 6 years] = £632.34, paid yearly

Justification of this particular software: This software was preferred by the majority of participants of a feasibility study. It also allows multiple contributors to edit the appearance of the questionnaire in real-time. Other important features include question skip logic, which allows only relevant questions to be asked to participants, thus reducing the overall time taken to complete the study and allows a better flow through the survey. Furthermore, Adobe forms lets use “help” buttons, headers and footers to give extra information to guide participants through the questionnaire without cluttering the page. Progression through the survey is clearly demonstrated with a percentage progress bar. It offers the research team the flexibility to add unlimited logos and images, which will aid parents to quickly identify the study, in addition to giving the questionnaire a more professional appearance.

These features combined give Adobe a superior survey experience for participants, which we hope will encourage parents to continue to return to the questionnaire for the whole duration of the study.

Email

Item Requested: 25,000 credits [=25,000 emails] at £157.67

Justification: MailChimp offers either a monthly subscription or a “pay-as-you go” option. Due to the frequency and volume of messages that will be sent by the LRBCS, purchasing credits is the most economical option, as the pay monthly option would cost upwards of £3400 for the whole study. The amount of credits requested pays for enough emails for the

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whole study (see email schedule) which accounts for a generous response rate of 20% (the predicted response rate for the study is 10%) and an attrition of 0% through the whole study. In the event of more emails being required, these can be purchased at a later date. The research team will re-appraise this number at the end of recruitment, when the total maximum number of emails can be calculated. Purchasing a sufficient amount of credits for the first year would not be economical, as 7,500 would cost £94.58, and considering that further emails would then need to be purchased, this would unnecessarily escalate the costs of the study.

An effective, professional and reliable email service is core to the success of the LRBCS, and it is felt that utilizing MailChimp is the only way the research team can be ascertain that this will be the case.

Postcards

Item Requested: 8,000 information and sign-up postcards to be distributed to all mothers of newborn infants born at Liverpool Women's Hospital. The estimated cost of this after researching the cheapest options is using:-

Print24 who will provide either 10,000 postcards A5, double-sided colour 250gsm, matt finish at £223.93.

It is cheaper to order postcards in bulk rather to buy batches of smaller quantities.

Justification: These are central to the research team's recruitment strategy. The NRES committee have approved the design and content of the postcard. The postcards must be A5 size in order to ensure they are legible. They must be in colour to encourage interest as it will significantly improve the aesthetic appeal, as well as ensuring that continuity between the stationary and the online forms. The finish needed will be either matt or silk finish in order to enable participants to complete their details in pen.

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Start-Up Cost

The estimated cost of start-up is £486.99, which includes the initial year's subscription to Adobe, the 10,000 postcards needed and 25,000 email credits.

Resource	Amount/Duration	Cost	Total
Adobe Forms Central Subscription	1 year	£105.39/year	£105.39
MailChimp Email Credits	25,000 email credits	£157.67	£157.67
Postcards (A5)	10,000	£223.93	£223.93
Total			£486.99

Total Cost

The total cost calculated for 6 years, which includes a 6 year subscription to Adobe, the 10,000 postcards needed and 25,000 email credits.

Resource	Amount/Duration	Cost	Total
Adobe Forms Central Subscription	6 years	£105.39/year	£632.34
MailChimp Email Credits	25,000 email credits	£157.67	£157.67
Postcards (A5)	10,000	£223.93	£223.93
Total			£1,013.94

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8. Postal Covering Letter and Consent Form



The Liverpool Baby Breathing Study

Dear Parent/Guardian,

Many congratulations on the birth of your new baby!

During your stay at Liverpool Women's Hospital, you spoke to a member of our research team and agreed to be contacted for our study. We understand that this has been a very busy time for you, so we really appreciate that you took the time to speak to us.

As you may recall, The Liverpool Baby Breathing study is a study that explores breathing symptoms, such as coughs, colds and wheezing in babies and young children. The aim of our study is to understand how these symptoms change over time, and how they affect you and your family. You can read a little more about the study on the first page of the enclosed questionnaire, under the "Further Information" heading.

If you are still happy to take part in the Liverpool Baby Breathing Study, please let us know by completing the attached consent form, and the first questionnaire (it only takes 5-10 minutes of your time!). We have enclosed a stamped envelope so you can return the questionnaire to us at your earliest convenience.

If you provided an email address when you registered your interest in the study, you may have received a link to an online version of the questionnaire. Don't worry, you don't have to fill it in twice – simply complete the online or paper version!

If you have any questions or concerns about the study, or are having problems completing the questionnaire, or would no longer like to participate in the study, please contact the research team directly and we will be happy to help!

We look forward to hearing your responses!

Best Wishes

The Research Team

Miss Rosanna Pickles

Miss Bethan Griffith

Dr Kevin Southern

Professor Ben Shaw

Dr Calum Semple

Email: babystudy@liverpool.ac.uk

Telephone: 01512824532

Post MG Semple, Institute of Child Health, University of Liverpool, Alder Hey Children's Hospital
NHS, Eaton Road, Liverpool, L12 2AP





Consent Form



Title of Project: Liverpool Baby Breathing Study (The Liverpool Respiratory Birth Cohort Study)

Name of Researchers:

Miss Rosanna Pickles, Miss Bethan Griffith, Dr Calum Semple, Dr Kevin Southern and Professor Ben Shaw

Please tick box

1. I confirm that I have read and understand the further information section dated 01/05/2013 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that our family and child's participation in the study is entirely voluntary and that we have the right to withdraw at any time without stating a reason and without affecting my care and my family's care in any way. ☐
3. I understand that the data collected by this study will be looked at by members of the research team named above and may be scrutinised by regulatory authorities or by the host NHS Trusts. ☐
4. I have read and understand the above consent form, I certify that I am the parent/guardian of the child recruited. ☐
5. I give permission for our family and my child to be involved in the above study. ☐

Child's Forename (first/given name): _____ **Surname:** _____

Your Child's Date of birth: Day: _____ Month: _____ Year : _____

Mother's Forename (first/given name): _____ **Surname:** _____

Mothers Signature for Consent: _____

Today's Date: Day: _____ Month: _____ Year : _____



9. LRBCS Email

Acknowledgement of contact details email



Liverpool Baby Breathing Study
Thank you for your interest!

Dear << Test Your First Name >>,

Congratulations on the birth of your new baby << Test Your Baby's First Name >>. We understand that this is a very busy and exciting time for new parents, so we really appreciate that you've taken the time to provide us with your contact details.

Don't worry, you don't need to do anything for now - we just wanted you to know that your contact details have been received by the research team. We will be in touch with when your baby is four months old with some more information about the study.

Our very best wishes to both you and your new family!

The Liverpool Baby Study Research Team

If you have any feedback, questions or concerns about the study, you can contact the research team by replying directly to this email, sending a message to BabyStudy@liverpool.ac.uk or by calling (0151) 282 4532.



[Add us to your address book](#)

Study Invitation Email



Liverpool Baby Breathing Study

Dear << Test Your First Name >>,

Congratulations on the birth of your new baby << Test Your Baby's First Name >>! During your stay at Liverpool Women's Hospital when your baby was born, you told us that you would be happy to be contacted about taking part in our research study.

Please click the link below to read the study information, and to access the first questionnaire - **it shouldn't take more than 5-10 minutes of your time!**

Your new baby's **UNIQUE ID** for the questionnaire is << Test Unique ID >> Please copy or write this down now as you will be asked for this at the start of the questionnaire. We use this for added security, and to help maintain your confidentiality!



Please click [HERE](#) to go to the first questionnaire!



Have any of your contact details changed since your baby was born?

If so, [please enter your new details here](#), or if you prefer, let us know by replying to this email.

What if I no longer wish to participate?

That's not a problem! We kindly ask that you let us know by replying to this email, or [remove yourself from the study by entering your email address here](#). Please note that your decision not to participate will not affect you or your child's future care.

Further information

You can find out more about the Liverpool Baby Breathing Study by visiting our website <http://pcwww.liv.ac.uk/~LRBCS/babystudy.htm>

We look forward to hearing from you!

Best wishes,

The Liverpool Baby Breathing Study Research Team

If you have any feedback, questions or concerns about the study, you can contact the research team by replying directly to this email, sending a message to BabyStudy@liverpool.ac.uk or by calling (0151) 282 4532.



[Add us to your address book - here's how!](#)

10. Document for Midwives



Liverpool Baby Breathing Study The Liverpool Respiratory Birth Cohort Study



What do we propose?

The Liverpool Baby Breathing Study (The Liverpool Respiratory Birth Cohort Study) is a longitudinal birth cohort study that will use the Liverpool Respiratory Symptom Questionnaire (LRSQ) to assess the respiratory symptoms of preschool children from birth to the age of 5. Parents will access the questionnaire by a link sent by email or paper copy by post. This study will map the natural history of respiratory symptoms of preschool children born in Liverpool.

When do we start?

Recruitment will begin in **January 2013**.

Who will we be recruiting?

All infants born at the Liverpool Women's to parents domiciled within the Liverpool postcodes, **L1-L38**.

How will we recruit?

Mothers will be given an **invitation postcard** during their admission. Postcards will contain a brief description of the study, and will include a space for parents provide contact details and basic information about their newborn.

What will happen with the postcards?

Mothers may either put the postcards in a collection box on the wards or researchers will collect the postcards from mothers. Alternatively mothers may register their interest by completing an online form accessible by scanning a QR code from the postcard or A4 Posters using their smartphone.



What will it involve for mothers?

- Mothers will be sent a questionnaire online or by post twice a year, for five years.
- The first questionnaire will be sent when the baby is 4 months old and should take no more than 10 minutes to complete
- Each subsequent questionnaire will be sent every 6 months and should take no longer than 5 minutes to complete
- All responses and personal details will be handled in the strictest confidence

If you have any questions or your patients would like to some more information?

Please contact please email **BabyStudy@liv.ac.uk** or call **(0151) 2824532** or visit **pcww.liv.ac.uk/~LRBCS/babystudy**



11. Access Information for LRBCS example questionnaire

It is not possible to demonstrate the functioning of the online questionnaire's advanced features on paper. To access and test the online version of the LRBCS please enter the following web link in to an internet browser (case sensitive): **<http://goo.gl/ZNOpi>**

When promoted, please enter "Test123" in the field asking for a unique ID code. Following this it will be possible to test the functions of the whole online questionnaire.

12. Paper version of LRBCS Initial Questionnaire



Welcome, and thank you for your interest in... Liverpool Baby Breathing Study

Questionnaire 1

The following questionnaire asks questions about your baby and what has been happening to him or her over the last three months. It should take **no longer than 10 minutes to complete**. All future questionnaires should take no more than 5 minutes to complete.

This study aims to find out more about the respiratory symptoms, such as wheezing, coughs and colds, that your child experiences, and how they affect you and your family.

Our study will help us understand what makes these symptoms more or less likely to occur and how they change over time.

It is important that every question is answered, even if your child has been perfectly well, with no problems at all.

Thank you.

Further Information

01.05.2013

Why have I been chosen?

We are asking all parents of children born at the Liverpool Women's Hospital who were living within the L1-38 post codes when their child was born to take part. We are particularly interested in the children of Liverpool as there are high levels of respiratory diseases such as asthma and bronchiolitis.

Do I have to take part?

No - it is up to you whether you decide to take part or not. You are free to withdraw at any time, without giving a reason. You and your child's future clinical care will not be affected if you do not wish to take part.

What will it involve (before/during/after?)

-We ask you to complete a questionnaire about your child. We will email you a link to the questionnaire just twice a year for five years.

-This questionnaire should take no longer than 10 minutes to complete.

-We will be asking you a few questions about your family circumstances, and your child's respiratory symptoms.

-You can choose to receive updates on how the study is running by email. At the end of the study, we will send you a summary of the results for the whole study.

Are there disadvantages of taking part?

We are not aware of any disadvantages to you or your child. All information will be treated with the strictest confidence.

Are there any advantages for taking part?

Being involved in the study will not benefit your child directly. We hope to help other children in the future by identifying what helps or worsens respiratory symptoms.

If you have any further questions, please contact the research team directly:

Email: BabyStudy@liverpool.ac.uk

Telephone: (0151) 282 4532

Please let us know if you would not like to receive any further contact from us, or if you want to go green and start receiving your questionnaires by email!





About Your Pregnancy, Birth and New Baby

You will only need to give us these details once

1. What is your new baby's first name?

2. What is your new baby's last name?

3. Is your new baby:

☐ Male ☐ Female

4. What is your new baby's date of birth?

5. What best describes your new baby's ethnic group or background?

- ☐ I would prefer not to say
☐ White - British
☐ White - Any other white background
☐ Mixed or multiple ethnic groups
☐ African, Caribbean or any other black ethnic group
☐ Asian - Indian, Pakistani or Bangladeshi or any other ethnic group
☐ Eastern Asian- Chinese or any other ethnic group
☐ Other - Please Specify

6. How many weeks pregnant were you when you gave birth? e.g. if you gave birth at 36 weeks 5 days , please write "36"

7. How much did your baby weigh at birth?

8. Did **you** smoke at *any time* during your pregnancy?

☐ Yes ☐ No

9. Did **any member** of your household smoke, *anywhere* or at *any time during your pregnancy*?

A household member means someone who sleeps or regularly takes meals at your house.

☐ Yes ☐ No

Where did these people smoke?

Tick all that apply

- ☐ Inside the home
☐ Outside the home
☐ Inside the car
☐ Inside at another location eg. work/social
☐ Other

10. Did you breast feed your new baby at any time? *This includes expressed breast milk or bottle feeding at the same time*

☐ Yes ☐ No

If yes, how long did you breast feed for?

☐ Less than 1 month ☐ 1-3 months ☐ I am still breast feeding





About You and Your Household

Your information will be stored securely and will not be shared

11. Which of these qualifications do you have?

- ☐ No qualifications
☐ Completed secondary school
☐ GCSE/O-Level
☐ Vocational Training/ Apprenticeship
☐ Diploma eg. BTEC, GNVQ
☐ A Levels/Scottish Highers
☐ Undergraduate Degree
☐ Postgraduate Degree
☐ Other (please specify)

12. Have you, your baby's father, or any of your baby's brothers or sisters ever been told by a doctor that they, or you, have of asthma, hay fever or eczema?

- ☐ Yes ☐ No

If you answered yes to the question above, who has Asthma, Hay Fever or Eczema?

	Asthma	Hay Fever	Eczema
Me (My baby's mother)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
My baby's father	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
My eldest child	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
My second eldest child	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
My third eldest child	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
My fourth eldest child	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

13. Does **any member** in your household smoke, anywhere?

A household member means someone who sleeps or regularly takes meals at your house. Please tick yes, even if they smoke outside

- ☐ Yes ☐ No

If yes, where do these people smoke?

Tick all that apply

- ☐ Inside the home
☐ Outside the home
☐ Inside the car
☐ Inside at another location eg. work/social
☐ Other

14. Does your baby attend nursery/crèche?

- ☐ Yes ☐ No





About Your New Baby

15. Do you have any other children who live with you?

☐ Yes ☐ No

If yes, how many other children live with you?

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 or more

16. Does your baby share a bedroom with yourself or anybody else?

☐ Yes ☐ No

If yes, who does your baby share a bedroom with?

Please tick all that apply

☐ Parent or parents ☐ One other child ☐ Two or more children
☐ Other

17. Has your new baby ever seen your GP because of his/her chest?

☐ Yes ☐ No

If yes, how many times has your baby seen your GP because of his/her chest?

☐ Once ☐ Twice ☐ Three times ☐ Four times ☐ Five times
☐ More than 5 times

18. Has your new baby ever been to hospital because of his/her chest?

☐ Yes ☐ No

If yes, how many times has your baby been to hospital because of his/her chest?

☐ Once ☐ Twice ☐ Three times ☐ Four times ☐ Five times
☐ More than 5 times

19. Does your new baby have any long term health conditions?

☐ Yes ☐ No

What kind of long term health condition does your new baby have?

☐ Long term chest (respiratory) disease?
☐ Long term heart disease?
☐ Long term kidney disease?
☐ Long term neurological disease?
☐ Diabetes?
☐ Other

Please tell us more about the long term health condition(s) your new baby has:



Your New Baby's Health

During the DAY(when awake) in the last three months::

20. My new baby has been wheezing (*whistling noise coming from the chest*)

- ☐ Not at all ☐ A few days ☐ Some days ☐ Most days ☐ Every day

21. My new baby has had a cough

- ☐ Not at all ☐ A few days ☐ Some days ☐ Most days ☐ Every day

22. My new baby has had a rattly chest (*noise that you can hear and feel as a vibration, when placing your hands over your baby's chest*)

- ☐ Not at all ☐ A few days ☐ Some days ☐ Most days ☐ Every day

23. My new baby has been short of breath

- ☐ Not at all ☐ A few days ☐ Some days ☐ Most days ☐ Every day

During the NIGHT (when asleep) in the last three months:

24. My new baby has been wheezing (*whistling noise coming from the chest*)

- ☐ Not at all ☐ A few nights ☐ Some nights ☐ Most nights ☐ Every night

25. My new baby has had a cough

- ☐ Not at all ☐ A few nights ☐ Some nights ☐ Most nights ☐ Every night

26. My new baby has had a rattly chest (*noise that you can hear and feel as a vibration when placing your hands over your child's chest*)

- ☐ Not at all ☐ A few nights ☐ Some nights ☐ Most nights ☐ Every night

27. My new baby has been short of breath

- ☐ Not at all ☐ A few nights ☐ Most nights ☐ Some nights ☐ Every night

28. My new baby has snored:

- ☐ Not at all ☐ A few nights ☐ Most nights ☐ Some nights ☐ Every night





Your New Baby's Health

29. How many colds (*runny nose, and high temperature*) has your new baby had in the last three months?

- ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ More than 4

When my new baby has **HAD A COLD** in the last three months:

30. My new baby has been wheezing (*whistling noise coming from the chest*)

- ☐ Not at all with colds ☐ A few days ☐ Some days ☐ Most days
☐ Every day

31. My new baby has had a cough

- ☐ Not at all with colds ☐ A few days ☐ Some days ☐ Most days
☐ Every day

32. My new baby has had a rattly chest (*noise that you can hear and feel as a vibration when placing your hands over your child's chest*)

- ☐ Not at all with colds ☐ A few days ☐ Some days ☐ Most days
☐ Every day

33. My new baby has been short of breath

- ☐ Not at all with colds ☐ A few days ☐ Some days ☐ Most days
☐ Every day

When my new baby has **NOT HAD A COLD** in the last three months:

34. My new baby has been wheezing (*whistling noise coming from the chest*)

- ☐ Not at all ☐ A few days ☐ Some days ☐ Most days ☐ Every day

35. My new baby has had a cough

- ☐ Not at all ☐ A few days ☐ Some days ☐ Most days ☐ Every day

36. My new baby has had a rattly chest (*noise that you can hear and feel as a vibration when placing your hands over your child's chest*)

- ☐ Not at all ☐ A few days ☐ Some days ☐ Most days ☐ Every day

37. My new baby has been short of breath

- ☐ Not at all ☐ A few days ☐ Some days ☐ Most days ☐ Every day



Your New Baby's Health

When my new baby has been more active (e.g. crawling, walking or when excited) in the last three months:

38. My new baby has been wheezing (*whistling noise coming from the chest*)

- ☐ Not at all ☐ A few days ☐ Some days ☐ Most days ☐ Every day

39. My new baby has had a cough

- ☐ Not at all ☐ A few days ☐ Some days ☐ Most days ☐ Every day

40. My new baby has had a rattly chest (*noise that you can hear and feel as a vibration when placing your hands over your child's chest*)

- ☐ Not at all ☐ A few days ☐ Some days ☐ Most days ☐ Every day

41. My new baby has been short of breath

- ☐ Not at all ☐ A few days ☐ Some days ☐ Most days ☐ Every day

Other problems my new baby may have had in the last three months:

42. My new baby has had noisy breathing that does not seem to come from the chest:

- ☐ Not at all ☐ A few days ☐ Some days ☐ Most days ☐ Every day

43. My new baby has had fast breathing:

- ☐ Not at all ☐ A few days ☐ Some days ☐ Most days ☐ Every day

44. My new baby has had noisy breathing that appears to come from the throat or back of the throat:

- ☐ Not at all ☐ A few days ☐ Some days ☐ Most days ☐ Every day



Your New Baby's Health

How my new baby's chest symptoms actually affected him or her over the last three months:

45. My new baby's chest symptoms have affected his or her feeding or eating
☐ Not at all ☐ A few days ☐ Some days ☐ Most days ☐ Every day
46. My new baby's chest symptoms have woken up my new baby:
☐ Not at all ☐ A few nights ☐ Some nights ☐ Most nights ☐ Every night
47. My new baby's chest symptoms have reduced my new baby's activity:
☐ Not at all ☐ A few days ☐ Some days ☐ Most days ☐ Every day
48. My new baby's chest symptoms have made my new baby unusually tired:
☐ Not at all ☐ A few days ☐ Some days ☐ Most days ☐ Every day
-

How my new baby's chest symptoms have affected *me and my family* in the last three months:

49. My new baby's chest symptoms have limited MY activities:
☐ Not at all ☐ A few days ☐ Some days ☐ Most days ☐ Every day
50. My new baby's symptoms have resulted in adjustments being made to our family life:
☐ Not at all ☐ A few days ☐ Some days ☐ Most days ☐ Every day
51. My new baby's chest symptoms have disturbed our sleep:
☐ Not at all ☐ A few nights ☐ Some nights ☐ Most nights ☐ Every night
52. I have been worried about my new baby's chest symptoms:
☐ Not at all ☐ A few days ☐ Some days ☐ Most days ☐ Every day





Your Details

Your data will be stored securely and will not be shared

You will only need to give us these details once!

53. What is **your** first name?

54. What is **your** last name?

55. What is your new baby's **father's** first name? *(optional)*

56. What is your new baby's **father's** last name? *(optional)*

57. What is your full address

58. What is your **postcode**?

59. What is your **main** telephone number?

60. What is your **main** e-mail address?

☐ I would like to receive my future questionnaires online

☐ I want to sign up to the Liverpool Baby Study newsletter to receive updates from the study





The Liverpool Respiratory Birth Cohort Study

Thank You For Your Participation!

All the information you give us is invaluable to the research team and future children in Liverpool, even if your baby hasn't had any symptoms at all! We will be in touch with you again in around 6 months time.

If you have any questions or would like to discuss the study with the research team, please don't hesitate to contact the research team at babystudy@liverpool.ac.uk or call us on 0151 282 4532

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